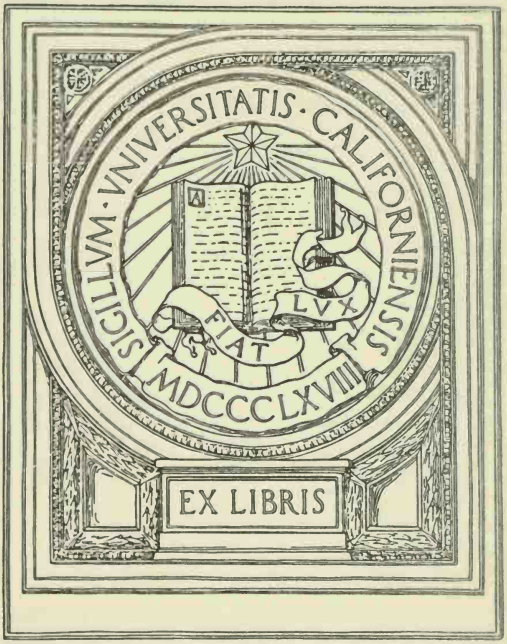
CHININUM



CHININUM

CHININUM SCRIPTIONES COLLECTAE

ANNO
MCMXXIV
EDITAE

AMSTELODAMI
MCMXXV

PREFACE

The interest with which our first publication:

CHININUM
SCRIPTIONES COLLECTAE, ANNO MCMXXIII
EDITAE

was received, has induced us to publish a second collection of a similar character. We have pleasure, therefore, in forwarding you a copy of same, trusting that it will find an equally ready welcome.

BUREAU FOR INCREASING
THE USE OF QUININE

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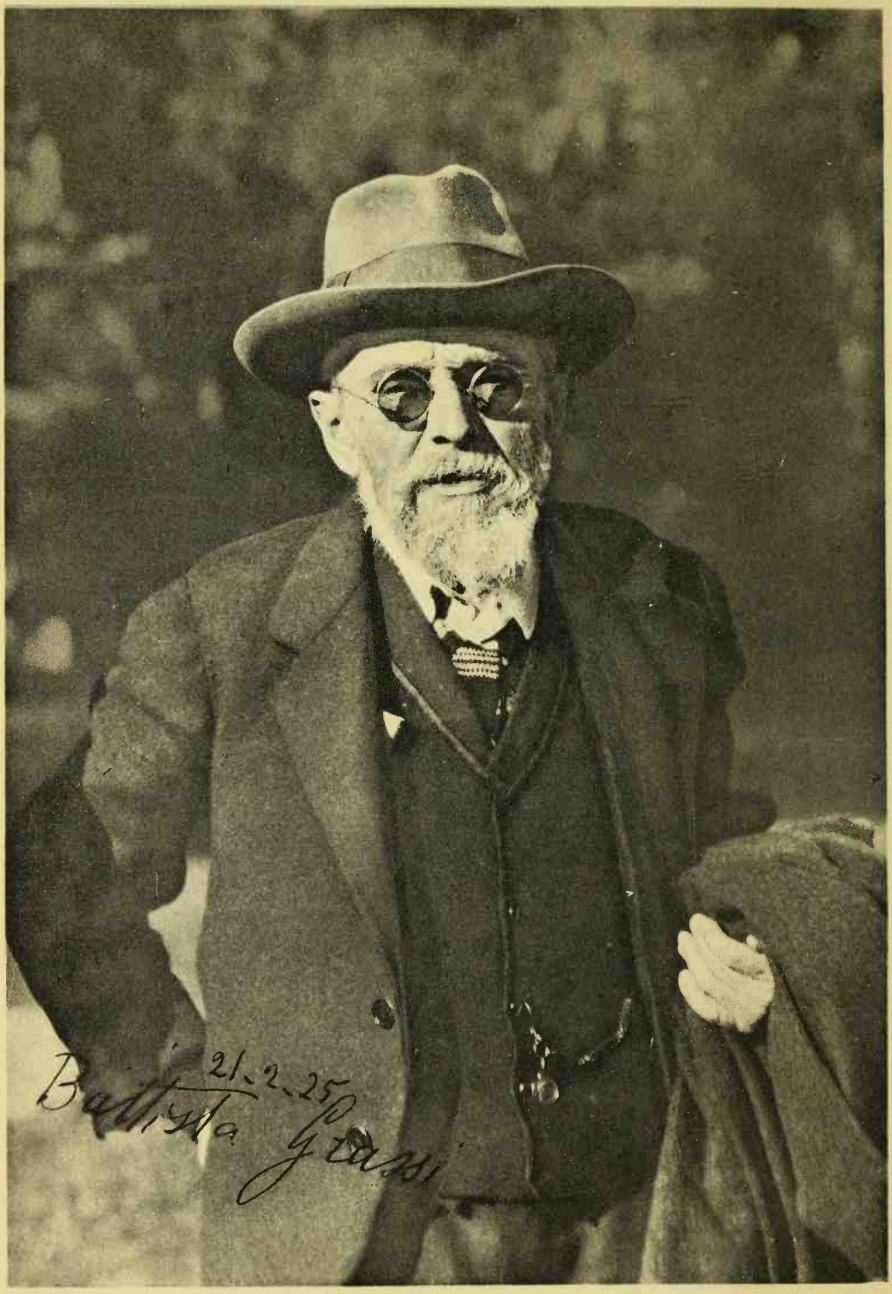

Plate I

Frontispiece

IN MEMORIAM

BATTISTA GRASSI

1854-1925

At the moment of publishing this work we have to fulfil the sad duty of paying homage to the memory of the great zoologist, Battista Grassi. His death deprives science of one of the most eminent specialists in malaria.

We cannot better express our great veneration for the deceased, than by inserting in our work an autographic reproduction of a paper which we received from him shortly before his death.

Risultati ottenuti dalla lotta antimalarica dopo la scoperta dell'Anofele malarifero.

In seguito alla scoperta dell'Anofele trasmissore della malaria la lotta contro questo flagello nell'Europa meridionale si è imperniata sulla bonifica dell'uomo, sulle protezioni meccaniche, sulla profilassi chinina e sulla piccola bonifica.

1°) Il malarico bonificato col chinino solo, o associato all'arsenico e al ferro, non contagia più gli Anofeli. Questa bonifica è agevolata dal lungo periodo (circa dal gennaio al giugno) in cui l'uomo è il solo depositario dei germi malarici, essendo gli Anofeli scarsissimi, pungendo poco o nulla e quasi mai diventando infettanti quando la temperatura è bassa; soccombendo tutti quelli dell'anno precedente al principio della primavera e rifugiandosi le nuove generazioni nelle stalle. Se in questo periodo interepidemico tutti gli uomini malarici venissero guariti, la nuova epidemia non si svilupperebbe.

2°) La protezione meccanica preserva dalle punture e quindi dalle nuove infezioni, mentre d'altra parte toglie agli Anofeli l'occasione d'infettarsi pungendo i malarici.

3°) La profilassi chinina, uccidendo non si sa bene come e quando i parassiti malarici innestati dagli Anofeli colle punture, previene lo sviluppo della malaria.

4°) La piccola bonifica, detta anche disanofelizzazione idrica, sopprime i minori focolai anofeligeni lasciati dalla grande bonifica, o prodottisi per negligenza, o per difettosa irrigazione, ricorrendo, per esempio, alla colmatura, ovvero

al petrolio, al verde di Parigi per distruggere la prole degli Anofeli in via di sviluppo. Vi si combina anche la disanofelizzazione aerea, ossia la soppressione degli Anofeli alati: la quale, se d'inverno non dà risultati rangibili, d'estate invece riesce molto proficua, potendosi in pochi istanti catturare per es. nei porcili centinaia di Anofeli, tra i quali la percentuale degli infetti è press'a poco come nelle abitazioni dei malarici.

Ognuno di questi metodi ha però le sue ombre.
1°) Molti malarici non si sottopongono alla bonifica soprattutto per sfiducia nel chinino, il quale, nonostante il lungo uso, non li ha liberati dalle febbri da essi ritenute recidive, mentre in realtà erano nuove infezioni. Certamente non mancano casi resistenti a questo farmaco divino, ma insistendo si finisce sempre per averne ragione.
2°) La protezione colle reticelle metalliche alle abitazioni da principio sembra fastidiosa ed è utile soltanto fino ad un certo punto, se chi se ne serve non ha anzitutto imparato a rispettarla e a usarla rigorosamente poichè essa permette di dormire colle finestre aperte e tiene lontane anche le mosche, tutti a lungo andare l'apprezzano.
3°) La profilassi chininica, che dovrebbe prolungarsi senza interruzioni per tutta la stagione malarica, non viene in pratica tollerata. È applicabile con profitto a persone che restano sul posto per poco tempo. Occorre però sempre assicurarsi volta per volta che il chinino venga veramente preso e deglutito

4°) La disanofelizzazione aerea ha applicazione limitata perchè spesso si trovano pochissimi Anofeli nelle camere dei malarici, che d'altronde mal volentieri lasciano entrare estranei. — Quella idrica trova ostacoli soprattutto nella circostanza che l'acqua anofeligena viene usufruita per l'irrigazione senza la quale la campagna diventerebbe sterile. Tuttavia l'acqua è fattore che favorisce ad un tempo la produzione del suolo e lo sviluppo degli Anofeli e quindi della malaria

× × ×

Dal complesso di queste difficoltà parecchi hanno dedotto che le nuove scoperte non hanno dato ancora costantemente i frutti che se ne attendevano. Quest'è un gravissimo errore. Nonostante tutte le deficienze che si deplorano nell'applicazione dei suddetti metodi di lotta, si raggiungono risultati che superano ogni ragionevole aspettativa. La morbilità malarica tocca sempre una cifra molto cospicua, diciamo pure enorme, ma le forme morbose sono relativamente molto meno gravi, le febbri di breve durata, la cachessia e la perniciosa infinitamente meno frequenti. Luoghi che durante la stagione malarica erano abbandonati da tutti e definiti campi della morte, oggigiorno vengono spesse volte coltivati da famiglie stabili le quali tollerano le febbri, ritenendole piccolo male, in confronto alla produttività del suolo. In luoghi

da cui trent'anni fa tutti fuggivano per non morire di perniciosa, al giorno d'oggi si teme più il tifo che la malaria. Insomma dapertutto lo spettro della malaria appare molto meno pauroso, anche là dove la grande bonifica non ha ancora fatta sentire la sua influenza.

Certamente, attenendosi ai nuovi dettami della scienza, si può fino ad un certo punto convivere cogli Anofeli. Che se queste norme vengano scrupolosamente messe in pratica, si può soggiornare finchè si vuole nei luoghi più gravemente malarici senza pericolo di contrarre la febbre.

Se si adottano le misure prescritte dalla igiene illuminata dalla scoperta dell'Anofele malarifero le opere di grande bonifica reclamate dall'agricoltura per la prosperità della Nazione si possono compiere impunemente, senza sagrifizio della salute umana.

E, quando si è giunti finalmente alla coltura intensiva del suolo, la malaria, come insegna l'esperienza dei secoli, scompare, ancorchè gli Anofeli persistano ancora numerosi — fenomeno del quale per ora non intendiamo bene la ragione

Non si perda però la chiara visione del vero stato delle cose. Ancorchè il flagello malarico in Italia siasi mitigato per la sua sterminata estensione i danni da esso prodotti sono ancora ingentissimi. Potrebbero tuttavia diminuire ancora più notevolmente, se la lotta contro la malaria con le armi che la scienza moderna ha affilate venisse intensificata. La spesa aumenterebbe, ma sarebbe certamente compensata da usura fortissima dai benefici che ne ridonderebbero come dimostra la campagna antimalarica che da otto anni vado sostenendo a Fiumicino. Non credo di esagerare asserendo che apporta un utile annuo sette volte maggiore del suo costo: ciò dal lato materiale. Del lato morale non occorrono commenti.

Roma 19 marzo 1925

Professore Battista Grassi
Senatore del Regno

RESULTS OBTAINED IN THE ANTI-MALARIAL FIGHT IN CONSEQUENCE OF THE DISCOVERY OF THE MALARIA-CARRYING ANOPHELES

(RISULTATI OTTENUTI DALLA LOTTA ANTIMALARICA DOPO LA SCOPERTA DELL' ANOFELE MALARIFERO)

PROF. BATTISTA GRASSI, ROME

Late Director of the Institute of Comparative Anatomy

IN consequence of the discovery of the anopheles, which is the carrier of malarial fever, the fight against this plague in Southern Europe has been based on the treatment of the germ-carrying man, on mechanical protection, on prophylaxis by means of quinine and on minor drainage and reclamation.

1. The germ-carrying man who is disinfected by quinine, alone or jointly with arsenic and iron, is no longer able to infect the anopheles. This way of anti-malarial fight is facilitated by the long period (from January to June almost) during which man is the sole carrier of the germs of malaria, because anopheles are rare; they sting very little and can hardly ever become capable of spreading infection when the temperature is low; all those of the previous year die at the beginning of spring and the new generations take up their abode preferably in cattle sheds. If, during this inter-epidemic period, all malaria sufferers could be cured, a fresh epidemic could not develop.

2. Mechanical protection by screens is a safeguard against stings, and consequently against new infections, while on the other hand it prevents the anopheles from becoming infected by stinging malarial patients.

3. Prophylaxis by quinine, by killing, we do not know when or how, the parasites of malaria inoculated by the stings of anopheles, prevents the development of malaria.

4. Small sanitation measures and drainage consisting in the destruction of watery breeding places of anopheles do away with small breeding centres of the latter (left over by large scale drainage or produced by negligence or faulty irrigation) by having recourse, for instance, to warping, or anti-larval measures (petroleum or Paris green), to destroy

the generation of the anopheles which is in process of development. To this there is added aerial anopheles destruction, that is to say, destruction of winged anopheles. This during the winter, gives no appreciable results, but during the summer, on the contrary, it is very successful, because in a very short time it is possible, for instance in pigsties, to capture hundreds of anopheles, among which the percentage of infected is almost the same as in the houses of malarial sufferers.

But each of these methods has its defects.

1. There are a number of malaria patients who will not submit to disinfection, above all owing to want of confidence in quinine, which, in spite of a long use, has not rescued them from the attacks which they take for relapses, while in reality they have been reinfected. Certainly there are subjects who are resistent to this wonderful remedy, but persistence is always succesful in overcoming this resistence.

2. The protection of houses by metal trellis work appears troublesome at the outset. It is only useful up to a certain point, if those who employ it have not learnt how to deal with the network, and to use it carefully. But as it allows of sleeping with open windows and also keeps away the flies, everyone ends by appreciating it.

3. Prophylaxis by quinine continued without interruption during the entire fever season is practically not tolerated. It can only be applied to advantage to those who remain in a given place for a specified time. Care must however be taken each time that the quinine is really taken and swallowed.

4. The aerial destruction of anopheles is of very limited application, for often but few anopheles are found in the rooms of malarial sufferers and the latter, on the other hand, do not like to permit strangers to enter their houses.

Aquatic destruction meets with hindrance, above all by reason of the fact that water containing anopheles is used for irrigation, without which the fields would become sterile. Unfortunately water is both a factor of fertilisation of the soil and of development of the anopheles, and through the latter, of malaria.

From all these difficulties several persons have inferred that the new discoveries have not given all the results which have been expected therefrom. This is a very grave mistake. In spite of all the inadequacies deplored in the application of the methods stated by me, results are obtained which exceed all reasonable anticipations.

Morbidity always reaches a very high, even enormous figure, let us say, but the morbid forms are relatively less grave than

before, the fevers do not last long, and cachectic and pernicious forms are infinitely more rare. Places which during the fever season were abandoned by everybody and called the fields of death, are to-day very often cultivated by families settled on the spot, which tolerate the fevers, considering them negligible in comparison with the productivity of the soil. In places from which, thirty years ago, everyone fled in order not to die of pernicious fever, typhoid is to-day more apprehended than malaria. Finally everywhere the spectre of malaria no longer inspires such great terror, even in those places where large scale drainage has not yet made its influence felt.

Certainly, by following up the latest rules of science, it is possible to a certain extent to share places of habitation with anopheles and if these rules are carefully practised one may reside in the most gravely infected places without danger of infection with fever.

To-day the large scale reclamation works which agriculture demands for the prosperity of the nation can be carried out with impunity without any sacrifice of human health, if the measures counselled by hygiene in consequence of the discovery of the malaria-carrying anopheles are adopted.

And finally, when intensive cultivation is reached, malaria disappears, as is shown by an experience of long standing, although the anopheles survive, a phenomenon the meaning of which we have not yet ascertained.

But we must not lose a clear vision of things as they now present themselves. Although the malarial plague in Italy has been effectively attacked, the damage which it occasions is still considerable in view of its immense extent. It may nevertheless be appreciably reduced if the fight against malaria with the arms forged by modern science were intensified. The expenses would increase, but they would be certainly made up for in practice by the benefits which might thence be obtained. This is what is shown by the anti-malaria campaign which I have been carrying on for eight years at Fiumicino. I do not think I exaggerate in saying that every year it produces seven times more than it costs; so much for the material side. As regards the moral side, there is no comparison to be made.

Rome, 19th March 1925.

THE LEAGUE OF NATIONS AND MALARIA

FIRST SESSION OF THE PERMANENT HEALTH COMMITTEE

Constitutional Questions.

THE first meeting of the new Permanent League Health Committee was held in Geneva from February 11th to February 21st, 1924. Dr. *Th. Madsen*, Head of the Copenhagen Serum Institute, was elected Chairman. The President of the *Office International d'Hygiène Publique*, at present Dr. *Velghe*, Head of the Belgian Health Service, was elected Vice-Chairman *ex officio*. Sir *George Buchanan*, Senior Medical Officer in the British Ministry of Health, and Surgeon-General *H. S. Cumming*, Chief of the United States Public Health Service, were also elected Vice-Chairmen for one year, thereby ensuring rotation among the members of the Committee without re-election. The Committee decided to submit the following names to the Concil for appointment as additional members:

Dr. *Chodzko*, former Minister of Health of Poland;

Dr. *Bernhard Nocht*, Director of the Hamburg Institute of Tropical Medicine;

Dr. *Alice Hamilton*, of Harvard University Medical School.

Malaria.

The Committee adopted the report of the Sub-Committee appointed last June (1923) to suggest methods of co-ordinating the campaign against malaria which is being conducted by a number of European states as a result of the aggravation of this disease in the years succeeding the war. A questionnaire drawn up in conjunction with malaria experts in the various countries is to be sent to the Health Administrations of European countries affected by malaria and the replies studied by a Sub-Committee composed of some members of the Health Committee and malaria experts co-opted from outside. The Health Committee will thus be in a position to furnish advice to governments which consult it on the subject.

Such advice has already been requested by the Albanian, Greek and Persian Governments. One of the Epidemic Commissioners has

already presented a preliminary report on conditions in Albania, and the Health Committee has now authorised a further and more extended investigation in both Albania and Greece, to enable it to furnish the Albanian and Greek Governments with the technical advice for which they ask.

The Persian Government's request involves a sanitary survey of the country as a whole, a measure which on technical grounds appears most desirable. Health conditions in Persia are important to surrounding countries, such as Turkey, Mesopotamia, Russia and India, particularly so in view of the Moslem pilgrim routes from the Far East to Mecca.

Quinine Supplies.

A further aspect of the problem of malaria now taken up by the Health Committee is the question of quinine supplies. If investigations by the League Health Organisation appear to warrant such a course, a conference may be held of representatives of the Health departments of countries in which malaria is an important and urgent problem, to consider the possibility of increasing the supply of quinine.

HEALT ORGANISATION

a. Advisory Council.

(The Committee of the Office International d'Hygiène Publique acts as the Advisory Council of the League Health Organisation).

b. Health Committee.

(Composed of sixteen members, namely, the Chairman of the Advisory Council, nine members chosen by the Advisory Council, and six members appointed by the Council of the League after consultation with the Health Committee. Four assessors may be appointed by the Council. The appointments extend over a period of three years).

Members:

Professeur *Léon Bernard*	(France)
Sir *George Buchanan, C.B., MD*	(Great Britain)
Doctor *H. Carrière*	(Switzerland)
Doctor *Carlos Chagas*	(Brazil)
Surgeon-General *H. S. Cumming*	(United States)
Doctor *A. Granville Pasha*	(Egypt)
Doctor *Jitta*	(Holland)
Professor *Ricardo Jorge*	(Portugal)
M. Shiko Kusama (provisional)	(Japan)
Doctor *Lutrario*	(Italy)
Professor *Madsen*	(Denmark)

Doctor *Mimbela*	(Peru)
Professor *Ottolenghi*	(Italy)
Professor *G. Pittaluga*	(Spain)
Doctor *L. Raynaud*	(France)
Doctor *Velghe*	(Belgium)
Doctor *Chodzko*	(Poland)
Doctor *Alice Hamilton*	(United States)
Professor *Nocht*	(Germany)

SECOND SESSION OF THE HEALTH COMMITTEE

The League Health Committee met from May 7th to 10th, 1924, in Paris. The following members were present:

Dr. *Th. Madsen*, President (Denmark); *M. O. Velghe* (Belgium), Sir *George Buchanan* (Great Britain) and Dr. *H. S. Gumming* (United States), Vice-presidents; Professor *Léon Bernard* and Dr. *L. Raynaud* (France); Dr. *H. Carrière* (Switzerland); Dr. *Chodzko* (Poland); Dr. *Jitta* (Netherlands); Professor *Ricardo Jorge* (Portugal); Dr. *Lutrario* and Professor *Ottolenghi* (Italy); Dr. *Mimbela* (Peru); Professor *B. Nocht* (Germany); Professor *G. Pittaluga* (Spain); Professor *Tsurumi* (Japan).

Completion of the Membership of the Committee.

The Committee decided to recommend to the Council of the League that Professor *Jean Cantacuzène* of the University of Bucarest, a member of the Office International d'Hygiène Publique and of the Central Committee of the Roumanian Red Cross, should be made a member of the Health Committee, as the representative of the Mixed Commission of the League of Red Cross Societies and the International Committee of the Red Cross.

The Anti-Malaria Campaign.

A definite plan was adopted for dealing with the question of malaria in Europe. This plan, prepared by a Sub-Committee that has been studying the question for some months, provides for a thorough investigation of the present position, both by malaria experts designated as corresponding members by the health administrations of countries in which malaria exists, and by an investigation on the spot by the Malaria Sub-Committee.

It is proposed to confine the work of the Committee to Europe as a beginning, although full advantage will be taken of the experience gained in fighting malaria in non-European countries. Reports are being submitted by corresponding members from Great Britain, Den-

mark and Holland, where malaria has been completely or almost extirpated within recent times, as well as from countries in South-Eastern Europe where malaria has always existed and has spread greatly since the war. The Sub-Committee is to visit Yugoslavia, Roumania, the Ukraine and Russia, returning to Italy, where the result of its investigations will be embodied in a report. The object of its investigations, which are merely preliminary, is not to furnish advice as to the best way of dealing with malaria, but to gain full and reliable knowledge of the actual situation in the countries visited.

At the request of the Albanian Government, Dr. *Haigh*, a former member of the League Epidemic Commission, who recently presented a report on the incidence of malaria in Albania, has been commissioned to complete the malaria survey in that country and to present a report, on the basis of which the Malaria Committee will prepare a technical plan for the use of the Albanian Government.

The World's Quinine Supply.

In connection with the work on malaria the question of the supply of quinine in relation to the world's needs as well as the medical efficacy of quinine and other cinchona alkaloids will be studied by a committee of five experts.

The Malaria Enquiry.

The League Commission for the study of the incidence of malaria in Eastern Europe began its tour of investigation in Yugoslavia on May 29th, 1924, and is to work for three months. The study in Yugoslavia lasted eighteen days, the Commission beginning at Zagreb, and gradually working south to Serbian Macedonia. It then crossed over to Greece for four days study in Greek Macedonia, went on to Bulgaria for six days, and then, until July 7th, to Roumania. From Roumania the Commission proceeded to Russia, arriving at Moscow on July 13th.

In Russia and the Ukraine the Commission is to study the principal malaria regions, namely the Ukraine (Kharhov, Bakhmut and environs); Northern Caucasus (Rostov, Piatigorsk and neighbouring health resorts); the Volga region (Tsaritsyn; from Tsaritsyn to Nizhni-Novgorod by boat along the Volga; Saratov, Pokrovsk, the German Volga Republic; Kazan and the Tartar Republic). From Nizhni-Novgorod the Commission will return to Moscow, where it will be shown the working of the Central Health Organisation and particularly the anti-malarial work of the Russian Health Service, and will take part in a conference on malaria.

Leaving Russia on August 4th, the Commission will proceed to

Italy to inspect the areas infected by malaria and to draw up a report on the results of the voyage.

Throughout the journey the Central Health authorities of the countries visited have conducted the party and shown it both the actual conditions in the areas infected with malaria and the measures taken to instruct and organise the Health Service for combating this disease. The Commission will, therefore, be in a position to make an exhaustive report on the whole question of malaria in Southern and Eastern Europe.

There are five members and seven experts or corresponding Members of the Commission, namely:

Members:

Dr. *Lutrario* (Chairman) (Italy); Professor *Nocht* (Vice-Chairman) (Germany); Dr. *Raynaud* (France); Professor *Ottolenghi* (Italy); Professor *Pittaluga* (Spain).

Corresponding Members:

Dr. *Markoff* (Bulgaria); Dr. *Marchoux* (France); Col. *James* (Great Britain); Dr. *Swellengrebel* (Holland); Professor *Ciuca* (Roumania); Professor *Marcinowski* (Russia); Dr. *Sfarcic* (Kingdom of the Serbs-Croats-Slovenes).

The Assembly, on September 20th, 1924, approved the report of its Second Committee on the Health Organisation, presented by Dr. *Caballero*, Delegate of Paraguay, and passed a resolution expressing its gratification at the fact that the Organisation had been definitely constituted, in accordance with the scheme approved by the Fourth Assembly, and was doing valuable work in promoting co-operation between the various countries on questions of public health. The development of the Service of Epidemiological Intelligence and Public Health Statistics as well as the establishment of a Far Eastern Intelligence Office at Singapore with the aid of funds generously supplied by the Rockefeller Foundation were specially noted.

The Assembly expressed its appreciation of the results obtained from the system of interchanges of officials.

It noted the results obtained by the work on the standardisation of sera and biological products, and by the various special enquiries, such as the cancer investigation and the Malaria Commission in Eastern Europe, as well as the fact that the Health Committee had placed investigators and technical advisers on Public Health questions at the disposal of various Governments requesting such assistance.

The Assembly expressed the opinion that the Health Organisation was fulfilling the duties assigned to it under the Covenant. It recommended that the Organisation should take up the problem of physical education and investigate the means for its general extension on rational principles, as well as undertake an enquiry into the value of preventive measures against tuberculosis.

THIRD SESSION OF THE HEALTH COMMITTEE

The Health Committee held its third session from September 29th to October 4th, 1924, at Geneva. The members present were:

Professor *T. H. Madsen*, Chairman (Denmark); Sir *George Buchanan*, Vice-Chairman (Great Britain); *M. O. Velghe*, Vice-Chairman (Belgium); Professor *Léon Bernard* (France), Dr. *Chodzko* (Poland), Dr. *Alice Hamilton* (United States), Dr. *Jitta* (Holland), Professor *Ricardo Jorge* (Portugal), Dr. *Lutrario* (Italy), Dr. *Mimbela* (Peru), Professor *B. Nocht* (Germany), Professor *Ottolenghi* (Italy), Professor *Pittaluga* (Spain), Dr. *Raynaud* (France) and Dr. *Tsurumi* (Japan).

On this occasion the Committee welcomed its new American member, Dr. *Alice Hamilton*, and Professor *Cantacuzène* who took their seats for the first time, and elected Professor *Léon Bernard* and Dr. *Lutrario* Vice-Chairmen, to hold office for one year from January 1st, 1925. The retiring Vice-Chairmen are Sir *George Buchanan* and Surgeon-General *H. S. Cumming*.

The Malaria Enquiry.

The Malaria Commission submitted a provisional report on its investigation in the Kingdom of the Serbs, Croats and Slovenes, Greece, Bulgaria, Roumania, Russia and Italy. The final report, which is being prepared for the end of this year, will contain exhaustive information as to the incidence of malaria and the methods used to combat it in all countries visited, together with conclusions and recommendations, and will be accompanied by special reports referring to each one of the countries visited.

At the same time, the Health Committee considered the first reports of its small Committee of Experts on the problem of quinine, and decided to recommend that attempts should be made in different countries to try the effect of the various cinchona alkaloids, of which quinine is only one. If other alkaloids, *e. g.* cinchonin, as well as quinine, could be used in malaria cases, the advantages would be obvious. The countries in which it is proposed to try the new methods are Algeria, Spain, Italy, and Roumania. The experiments will be conducted under the auspices of the Malaria Commission and with the aid of material fur-

nished by the Commission so as to ensure uniformity of conditions. The Malaria Commission will continue its study of the incidence of malaria in Europe by establishing relations with experts and corresponding members and by an investigation in Sicily, Tunis, Algeria, Morocco, Spain and Portugal in 1925.

The Council accepted the invitation of the Italian Government for the Health Organisation to send a representative to co-operate in the work of the first International Congress on Malaria which will be held at Rome , 4th-6th October, 1925.

(*Monthly Summary of the League of Nations,* Geneva, **4**: 1924, pp. 35, 36. 45, 90, 112, 113, 181, 226, 228, 273)

MALARIAL fever is important not only because of the misery which it inflicts upon mankind, but because of the serious opposition which it has always given to the march of civilisation in the tropics. Unlike many diseases, it is essentially endemic, a local malady, and one which unfortunately haunts more especially the fertile, well-watered, and luxuriant tracts — precisely those which are of the greatest value to man. There it strikes down not only the indigenous barbaric population but, with still greater certainty, the pioneers of civilisation — the planter, the trader, the missionary, and the soldier. It is therefore the *principal and gigantic ally of Barbarism*. No wild deserts, no savage races, no geographical difficulties have proved so inimical to civilisation as this disease. We may also say that it has withheld an entire continent from humanity — the immense and fertile tracts of Africa; what we call the Dark Continent should be called the Malarious Continent; and for centuries the successive waves of civilisation which have flooded and fertilised Europe and America have broken themselves in vain upon its deadly shores.

SIR RONALD ROSS

Plate III

Ronald Ross

17 March 1925

THE JOURNEY OF THE MALARIA COMMISSION OF THE LEAGUE OF NATIONS TO EASTERN EUROPE AND ITALY

(DE REIS DER MALARIA-COMMISSIE VAN DEN VOLKENBOND NAAR OOST-EUROPA EN ITALIË)

PROF. DR. N. H. SWELLENGREBEL, AMSTERDAM

From the Institute for Tropical Hygiene – Department of the Colonial Institute in Amsterdam

(With map showing the itinery and 13 photographs)

THE "Malaria Commission" is a component part of the Committee of Hygiene of the League of Nations, a sub-committee formed by a few members of the said Committee, assisted by two "experts" and a number of "corresponding members" selected in countries where malaria is of importance, or forms a subject of study.

The special interest in malaria dates from the war and post-war years, when the great wave of malaria in the whole of Europe (even in England) awakened anew the general interest in this so-called "solved problem". This led in many countries to a renewed struggle against malaria, but not all were able to defray the necessary expense, and thus Albania appealed for the help of the League of Nations. The Sub-Commission for Malaria was entrusted with the task of investigating what measures it would be best to recommend to this and other countries, which are not able to allocate much in their budget to this purpose. The question therefore: How can malaria be combated in the cheapest way?

Now in a case like this the first point must be to agree on what is meant by "combating malaria", otherwise the matter will degenerate into merely idle discussion. The meaning may be: 1. The eradication of malaria so that, after some time, the work may be stopped without new cases occurring unless imported from outside. 2. Reducing its extent and the gravity of its consequences without aiming at destruction of the potential capacity of the country and people in and among which the work is done, to produce malaria. This latter is in most instances wondrously successful, and more strikingly so the graver the previous condition. It is even possible without human aid, but

with this the process may be hastened and the suffering meanwhile reduced.

In times of acute and severe epidemics with high mortality, it is felt to be highly satisfactory merely to secure this latter measure of success, by means of quinine treatment, sometimes assisted by measures against the anopheles. But when the epidemic is over the wish makes itself felt to get rid altogether of this threatening epidemic danger; a wish which manifests itself even among those residing in a country where malaria takes the form of epidemics which, though not dangerous, are nevertheless unpleasant, as for instance in our own country. Then, the aim is not merely to treat the sufferers, but to attack the evil at its roots, by the destruction of the parasites in the human blood or of the transmitting mosquito, as larva or adult in water or air. This is, in part, what was already done in the epidemic period. But in this instance it is too frequently found that no great success is achieved. The malaria level has, after the drop, come to be more or less fixed and often is no longer to be shifted — till the time it rises once more or possibly, for some unknown reason, gradually drops to the zero point.

What then is the object of the Malaria Commission? The cheapest measures for combating acute epidemics or those for eradicating the chronic endemics left behind? In the nature of the thing, both: What requires to be done for combating acute epidemics is really well known: quinine distribution among the population in such manner that it is applied in the most effective possible way. But to eradicate malaria by means of quinine is not feasible. Moreover, unfortunately, other means which our modern knowledge places at our disposal, are often found to be inadequate. Yet we see that in some countries malaria has entirely, or almost, disappeared. "For some unknown reason", as I said above. The Malaria Commission, at the proposal of its expert, Colonel *S. P. James,* set before itself the aim of filling up this gap in our knowledge. The plan was to collect information about malaria in countries where this disappearance of the illness had been observed, namely: in England, Denmark and Holland. He travelled through these three countries, which were subsequently invited to present a report dealing with the question of how matters stood previously as regards malaria, how it now stands and what, in the opinion of the reporters, was the reason of the change eventually observed. These reports, with their conclusions, are to be published and I therefore do not desire to anticipate them. So much I can say however, that it was found generally, on critically examining the historical data, that it was exceedingly difficult to form an exact idea of the conditions as regards malaria in earlier times. The view shared by many however, is that such disap-

pearance or considerable decline in importance of malaria must be ascribed to a series of factors. One of them is the greater penetration of quinine into larger masses of the people. There are others however (and according to some, of the first rank), such as increased prosperity, expressed in better feeding and housing; increased store of cattle, etc. It is difficult to convert these factors into advice, for obviously it is of little use to say to a country like Albania, for instance: "Go and get rich".

Another plan of the Malaria Commission which found its initial realisation in the journey carried out this spring and summer to Eastern Europe, was to make a comparative enquiry into the measures applied in various Eastern European countries against this disease. It may be asked whether this journey was really necessary and whether extensive reports, quietly studied at home, would not have been just as good and considerably cheaper. They would never of course have been able to take the place of a long continued investigation on the spot, but this journey could not give the opportunity for such investigation either.

In my view this would not have been equally good: We cannot understand these reports because we do not know the language of the country. I do not mean by this because we know no Serbian or Russian, for the reports are drawn up in French or some other readable language. But those Serbians or Russians say things which, of necessity, we misunderstand, unless by personal intercourse and inspection we have got to know what is meant by them. Let me endeavour to make this clear by an example.

Last year, during a journey for the study of malaria in Italy, a good deal of time was devoted to inspection of the "bonifications" which are, in many respects, comparable with our "polders". Now I do not believe that we should ever think of mentioning our "polders" as examples of malaria combating, as we know very well that the ditches there are excellent breeding places for the anopheles. Now, if we observe that Italy does not differ in this respect, that after the drainage, with its consequent growth of population, malaria, in the absolute sense at least, increases, then the association of the two things, malaria combating and marsh reclamation, is seen to be misleading. Anyone who has not been there himself and has not seen with his own eyes that the anopheles breeds merrily in the ditches and occurs just as much in houses and stables as in the still unreclaimed territory, will naturally think that it needs only the drainage of marshes in his own country in order to get rid of malaria. But when we come to realise how this thing has grown up in Italy, we get an

entirely different view of the whole and we see that our first judgment was really incorrect. These attempts at reclamation were strongly supported by the Italian malaria experts; at their instigation the law was passed by which such works, when considered to be of general interest on hygienic or economic grounds, are supported by state subsidies. Moreover, many were influenced not solely, and even not chiefly, by the argument that by such reclamation the larvae would be controlled, but that welfare would thereby be promoted, the population would receive better feeding and better housing and that this reacts favourably on malaria. Even if the number of cases may not change, there is the change as to their gravity (lower mortality). All this of course applies only to the case where the reclamation is valuable from the economic standpoint.

Two views continue to this day to exist side by side as to the utility of reclamation. One lays stress on the direct anti-larval effect, but admits that, as such it will be of no avail, and demands legal enactments to compel the landowners to keep their ditches free of larvae. The other maintains that it is of use, lays stress on the indirect, or the economic effect and smiles pityingly when it is pointed out that there are still larvae: for that is not the point.

It must not be thought that these two motives for executing reclamation work are ever sharply separated from each other; you are compelled, as it were, to filch the secret from the people simply because they do not understand what can possibly be obscure to us, as foreigners, in this matter which to them, who were born and brought up in it, is as clear as daylight.

In another country, not to be mentioned here, where these fine distinctions are not known, it was decided, that malaria has been fought in Italy by reclaiming marshes. What is meant here is the immediate effect and the indirect is not considered. The law there simply prescribes that districts declared to be infected with malaria must be subjected to extensive reclamation at State expense and to minor works at the expense of the landowners. The economic side of the question is not mentioned: the reclamation is directed against the larvae. And that is precisely its weak point; if too much relied on, it often brings disappointment.

I must admit that I only came to realise the Italian standpoint thoroughly after my visit to that other country, where it is so completely misunderstood. But is it not necessary then, that this and similar misunderstandings should be cleared away? For there are others, not all so far reaching and at the same time involving such fine distinction as the one here mentioned, which result in measures being

praised highly in one country, while in another they lead to nothing but disappointment.

To ascertain the existence of these misunderstandings, to expose their causes and to endeavour to prevent them in future as far as possible by international co-operation, appeared to be the real object of our journey, rather than that indicated above: comparing the value of the measures applied in the various countries, because such comparison, precisely by reason of the above misunderstanding, was frequently so difficult to make.

Below I propose to give a brief survey of what we saw and what we were told, not however in the form of a connected narration of events, but by grouping together facts under their respective heads:

1. Our route.
2. Organisation of the fight against malaria.
3. To what extent malaria occurred in the different countries.
4. What was the nature of the malaria there.
5. The importance and the use of quinine in the struggle against malaria.
6. The same in the struggle against anopheles (mosquito and larvae).
7. Conclusions to be drawn in relation to malaria in Holland.

1. *Company and route.*

As the president of our Commission, Dr. *Lutrario*, only shared our journey in Italy, our president for the hardest part of this journey was Professor *Nocht* of Hamburg, who, together with Colonel *S. P. James*, the wellknown British Indian expert in malaria, were our highest authorities in this department. Beside them there were Professor *Ottolenghi* of Bologna and Professor *Pittaluga* of Madrid. Finally, there were present as corresponding members, Professor *Ciuca* of Jassy (Roumania), Dr. *Anigstein* of Warsaw (Poland) and myself. In some countries we were also accompanied temporarily by some of our corresponding or ordinary members who did not share the entire journey; among these were Professor *Marzinowski* of Moscow, in Russia and Italy, Professor *Marchoux* of the *Pasteur* Institute and Dr. *Raynaud* of Algiers, in Italy. (Plate XXIII; p. 265).

Our company gathered on the 27th May 1924 at Zagreb *(Croatia)* and from there went to Kraljevica on the Adriatic coast near Fiume, from where we visited the neighbouring island of Krk. Here we made acquaintance with the peculiar malaria question in the barren and bone-dry region of Karst, where man is the cause of malaria, because he and his cattle are so unpractically built that they cannot live with-

out water (i.e., something like what happens in Jerusalem). Almost all available water (except in the rain wells, of which there are not enough) is there found in the "lokva's", which are artificial or, at any rate, artificially maintained pools, frequently heavily overgrown with plants, the water of which is used for washing and for watering cattle, — sometimes man also. They are at the same time the only breeding places of anopheles. (Plates IV & V).

On 2nd June we arrived in Sebenico, situate further south in *Dalmatia*, on the Adria. The surroundings, the same barren, treeless, inhospitable region of Karst, which we visited in the following days, again raise the same lokva question as on the Island of Krk, for, apart from the valleys of a few brooklets and the marsh near Vrana, there is no water here. Matters were quite otherwise however at the mouth of the Neretva near Metcovic, where a genuine inundation area with many breeding places and masses of anopheles in houses and stables, made a much more serious impression than Karst. Yet there was much less malaria here (spleen index 50 per cent.) than in the last mentioned region (spleen index 90 per cent.).

On the 8th June we reached Sabac on the Save in *Slovenia*, likewise a genuine inundation territory, with a fair amount of malaria, not of a grave character. In order, finally, to travel through Serbian Macedonia, we, on the 10th June, arrived at Skoplje (Üsküb), on the 12th in Veles (Köprülü), on the 14th in Bitolj (Monastir), from which places we visited the environs, such as Prizren, Stip, Kocani and Struga. Here we were on one of the grounds of the world war, where there had been most suffering from malaria, which however was now everywhere in process of decline.

In Salonika on the 16th June, we came into contact with the consequences of the "interchange of population", as it is euphemistically termed: Fully a million Greeks, expelled from Asia Minor and Thrace; families which had lived there for generations, which arrived, with nothing but the clothes they wore and absolutely poor, by hundreds together in Salonika, where they were temporarily put up in 5 big camps, each containing 6 to 10.000 inhabitants, until they were settled as agriculturists (and how many of them understand anything of this trade) in the valleys of Vardar and Struma, from where, to make room for them, 400.000 Turks in turn were shipped to Asia Minor. Among these immigrants, both in the camps around Salonika and in the villages, severe malaria prevails, or rather prevailed, because this year it was also declining. Whether the immigrants brought this malaria with them, as some think, or that the illness occurred endemically in those river valleys and they were badly attacked by it as not being

Plate IV

DALMATIA
Lokva's; original aspect

Photo Dr. Svarcic, Trogir

Plate V

DALMATIA

Lokva's rendered harmless; work not yet completed

Photo Dr. Svarcic, Trogir

acclimatised, which in turn reacted upon the population, who can now determine with certainty, by reason of the impossibility of a calm investigation during such chaos? The only thing was treatment, the saving of lives. There was therefore not much to be learned here, except as to what is to be expected in such migrations, when the fine conditions of balance in Nature are disturbed. We saw the camps around Salonika, the valley of the Vardar with Yanitza, that of the Struma with Seres, all with villages containing 50 to 90 per cent. of refugees, and on the 21st we proceeded to Sofia.

In *Bulgaria* likewise where we stayed from the 22nd to the 28th June, we found malaria strongly declining. We visited the Maritza Valley, with the extensive ricefields and the coastal lakes of Burgas and Varna. Here more than anywhere (except in the Karst region) the solution of the malaria problem is sought in anti-larval measures, on which, in large and small reclamations, artificial salting of coast lakes and the like, millions of levas are spent.

Just the opposite is found in *Roumania* (28th June to 7th July) where we visited Wallachia minor and the environs of Bucharest and Galatz. The nature of the land, with the recurrent overflows of the Danube and her tributaries, furnishes a wealth of breeding places, such as there can be no thought of clearing up. All anti-larval measures therefore have been disregarded, and salvation is sought in systematic quinine treatment of the population, by which, before the war, it is thought that favourable results were obtained, but which is now made very difficult, owing to the lack of country doctors, of whom one-fifth died of typhus.

In *Russia* (13th July to 8th August) we felt it to be a great difficulty, that the Commissariat of Public Health could do, as yet, so little for the agricultural population. Malaria is, first and foremost, a disease of the country; as we were constantly referred to towns or artificial aggregations of population, it was really impossible to form anything like a just idea of the malaria.

We visited a part of the Ukraine and the Don territory, where the malaria had increased in 1924, during the first five months as compared with 1923, but fell off again in June. Also the mineral baths of the Northern Caucasus and the Volga territory from Tsaratsin to Nijni Novgorod. Nothing more was to be seen of the frightful conditions which must have prevailed last year everywhere on the Eastern bank ("meadow bank") of the Volga when, on market days, entire convoys of sick were conveyed to the malaria stations and it might have been imagined that a great battle had been fought somewhere in the neighbourhood.

The northern portion of the territory visited by us (Kazan, Nishegorod, Moscow) was still exceedingly interesting, inasmuch as we here reached territory where tertian prevailed, a territory therefore to be compared in many respects with our own country. But it differs from the latter owing to the less favourable conditions in which a large portion of the population found itself, in consequence of famine and other circumstances, among which, above all, the lack of quinine may be mentioned, a lack which is no doubt now beginning to be less urgent, but still exists. When we call to mind the stories to be found in the older literature on epidemics of intermittent fever in the Netherlands, the experience in Russia makes it distinctly easier for us to accept a part of these stories as true, while another part, in which very high mortality is mentioned, becomes still more unintelligible because, in spite of the epidemic being so virulent, the death rate was low there.

In the environs of Moscow we were very much interested by the great peat moors, of which we saw one at Chaturka. They arose during the blockade when there was a lack of all fuel and peat had therefore to be used. The said peat moor supplied this year 240 million kilos of peat and is worked by fully 6000 labourers, who are there from May to the middle of July and come mostly from the Province of Riasan. In 1922 there was still a good deal of malaria, which fell off in 1923 (just when the epidemic reached its climax in most regions), and still more in 1924. This went along with strong quinine treatment of the labourers, both on the land itself (with 1 policlinic, 2 hospitals and a malaria station with 2 doctors and 5 students) and at the place of origin. Every year fresh engagement of the people for the work is preceded by a medical examination.

In *Italy* (14th to 28th August) we inspected the malaria control measures in the region of the Piave, where many reclamations destroyed by the war have been restored and new ones added. This, during the carrying out of the work and for some years after it, at times results in a revival of malaria among the navvies and the first agricultural inhabitants, as was unpleasantly observed this year. Why things are so much better in the older drained lands is not clear; it is certainly not by reason of the lesser number of anopheles met with there.

In the environs of Rome we saw the Pontine Marshes, with the ambulances of the Red Cross for the distribution of quinine among the population; the polders around Ostia, where the Commune of Rome has the medical direction and it is sought to keep the ditches free from larvae by means of Gambusia affinis; Nettuno, the malaria school, where Professor *Gosio* is training the auxiliary staff required for

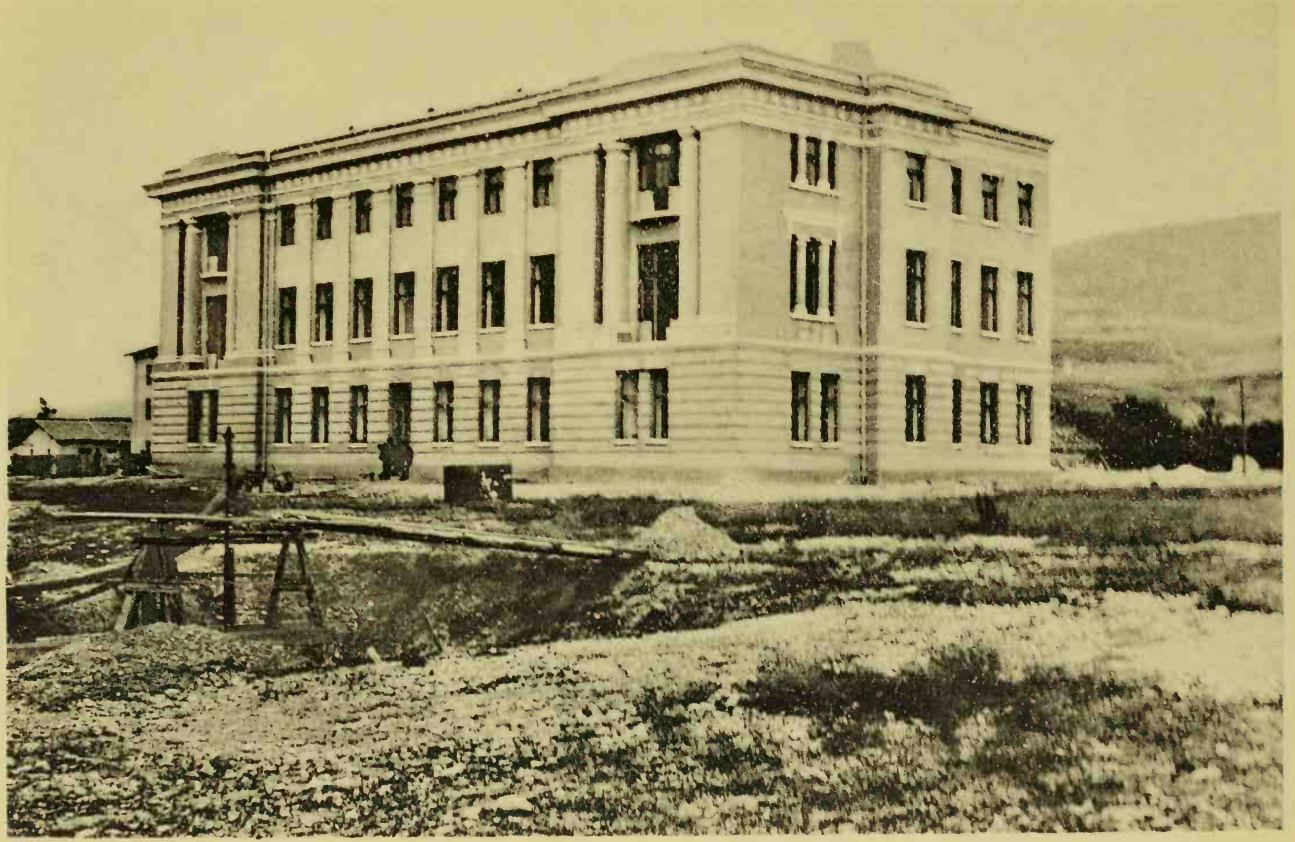

Plate VI

SERBO-MACEDONIA
Institute for Tropical Diseases, Skoplje

Photo Prof. Ciuca, Jassy

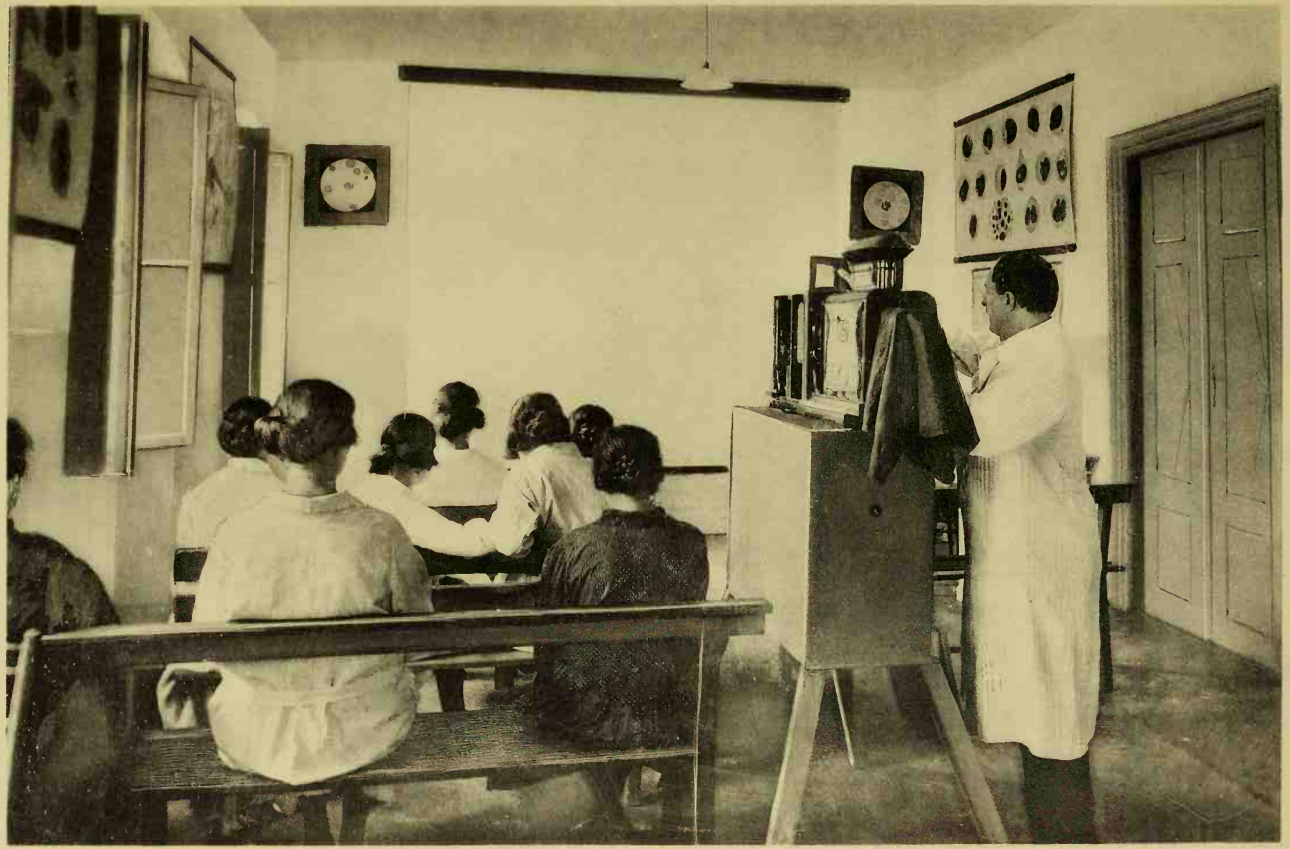

Plate VII

DALMATIA

School for training of auxiliary staff, Trogir

Photo Dr. Svarcic, Trogir

fighting malaria; Bocca di Leone, the country estate where all breeding places of anopheles were cleared away by underground drainage. Finally, we made a pilgrimage to Fiumicino in order to see old *Grassi* once more on the land of his activity. I was acquainted with all this from last year, but it was the more interesting to me, above all because everywhere, just as in the Piave territory, some revival of the malaria was reported. This terminated the journey, which had lasted 3 months.

2. *The organisation and cost of fighting malaria.*

In *Serbia*, the second division (that of hygiene) of the Ministry of Public Health, which is entrusted with combating contagious diseases, is financially self-governing. Its medical officials may, subject to approval of the chief of that department, carry out measures of all kinds, independently, and even impose fines, not exceeding 6000 dinars without recognising the civil administration. This department has for its centre the Central Epidemiological Institute in Belgrade, the director of which is at the same time the chief of the department and to which a school for training hygienists and a hospital for infectious diseases are attached. Under him there are the 4 already existing epidemiological institutes, 21 bacteriological stations, special institutes for combating tuberculosis, venereal diseases, trachome and malaria.

Malaria fighting is therefore a separate sub-service, the headquarters and the chief of which are to be established in the (almost completed) "Institute for Tropical Diseases" at Skoplje. (Plate VI). Under this authority fall: the malaria institute of Trogir for *Dalmatia, Herzegovina* and *Montenegro* with auxiliary stations at Cettinje and Metcovic; the bacteriological station of Kraljevica for the *Croatic Islands* Krk, Rab and Pada; bacteriological stations of Sabac and Belgrade with 5 flying columns and a few auxiliary stations for the plains of the Danube and Save, and finally in *Southern Serbia*, the malaria institutes of Stip and Struga and the bacteriological stations of Skoplje, Novi Bazar, Prizren and Bitolj with a further 14 auxiliary stations.

The oldest institute and the one most developed in organisation is that of Trogir in *Dalmatia*, on the Adriatic coast north of Spalato. It was opened in July 1922 and has a school for the training of an auxiliary staff (1 year's course). (Plate VII). In 1924 it worked in a territory with 230 villages, distributed among 26 "endemic doctors", assisted by 53 male and female assistants and 2 "disinfectors". Each endemic doctor once or twice a week or month, visits all villages in his "malaria district", while the daily distribution of quinine is entrusted to schoolmasters, priests, or burgomasters. The blood examination is carried

out in small auxiliary stations (only microscopic and stains) by the assistants. For conveyance, motor cars are available.

The other institutes are organised in a similar way: Stip (*Macedonia*) for instance, has, for a population of 200,000 souls, 6 auxiliary stations, 6 free consultation offices (Plate VIII) and 2 motor-car laboratories. (Plate IX). The bacteriological stations are somewhat smaller: Kraljevica, for example, has 3 doctors, 4 students of medicine, some assistants for laboratory work and as quinine distributors, 17 teachers and priests and 2 farmers. Apart from the distribution of quinine, also anti-larval and mosquito work is carried out in these centres, especially at Trogir and Kraljevica.

The budget for the malaria service for 1924-1925 is 10 million dinars, including 3 million for the construction of the institute at Skoplje.

An apparent agreement, together with a penetrating difference from the foregoing is shown by the organisation of the service of malaria control in *Russia*. The general direction here comes from the Central Malaria Commission of Moscow through the medium of the Commissariat for Public Health. This Commission, which includes representatives of all Commissariats of the People, creates unity in the work of the many sub-sections and other co-operating services, collects answers to enquiries and distributes that portion of the quinine which the Union supplies free of charge or which is sold; it opens new malaria stations, prepares laws and every year organises the Pan-Russian Malaria Congress. The following are subject to its direction:

1. The provincial malaria commissions, in many respects a miniature reproduction of the first, serving chiefly to harmonise the operations of various services. Doctors and representatives of various groups of workmen have seats on this commission.

2. The executive institutions proper, the task of which is to treat sick cases reporting themselves, in some instances to search them out, particularly in childrens' homes and among factory workmen, soldiers and pupils of some educational institutions. "Visiting the peasants", which is in Serbia the chief task of such institutions, only occurs here occasionally in the form of detachments or expeditions sent out. Of a regular visit to all villages situated within the territory of a malaria station there is no question. Each person who reports himself at one of the chief stations has his blood tested, but in the auxiliary stations, this is only done in doubtful cases or not at all. From what part of the population those who attend emanate, is not known. The territory of work proper remains the town. These institutions are:

a. The 5 institutes for tropical diseases in Moscow, Kharkov,

Plate VIII

SERBO-MACEDONIA
Public consultation office, Trabatovitehc

Photo Dr. Alkovitch, Stip

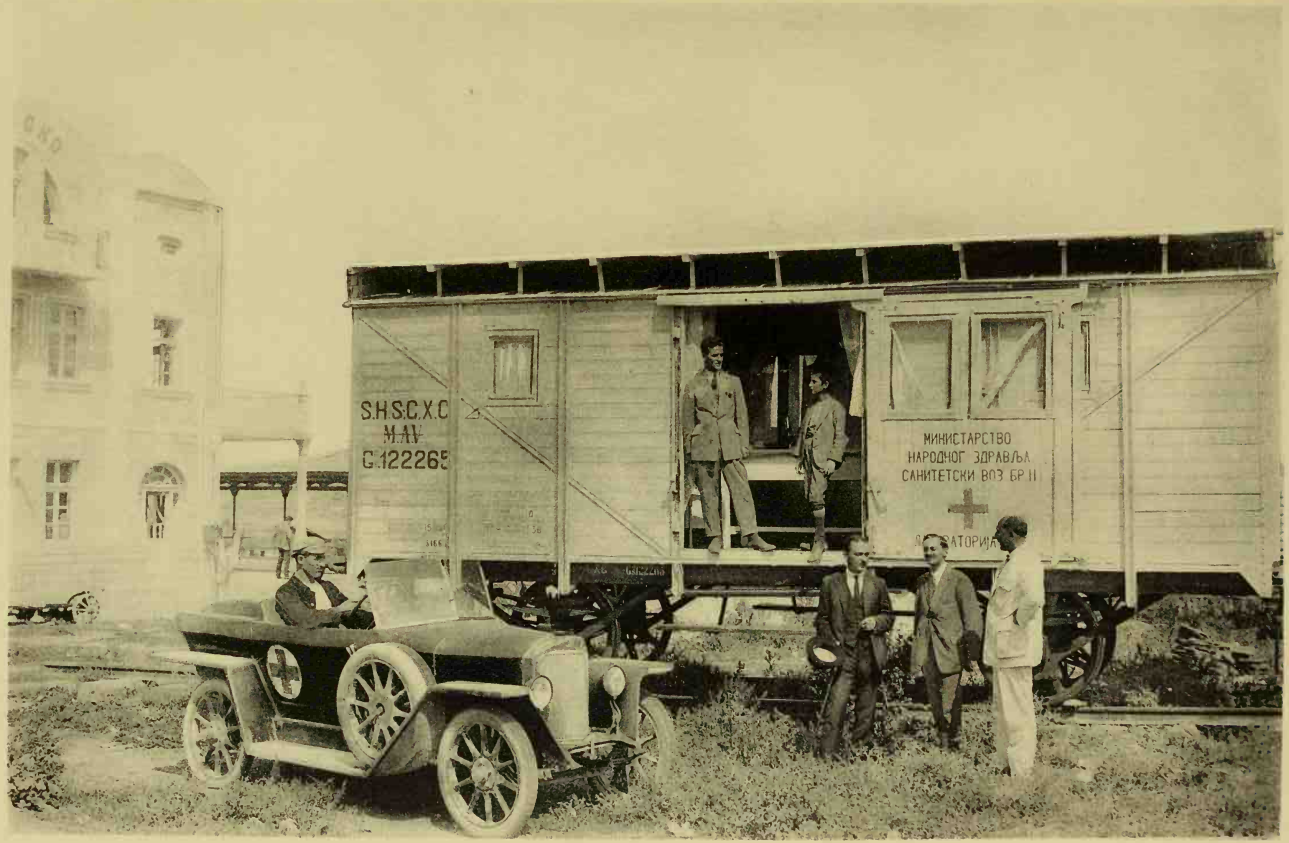

Plate IX

SERBO-MACEDONIA
Railway laboratory carriage, Gradsko

Photo Dr. Alkovitch, Stip

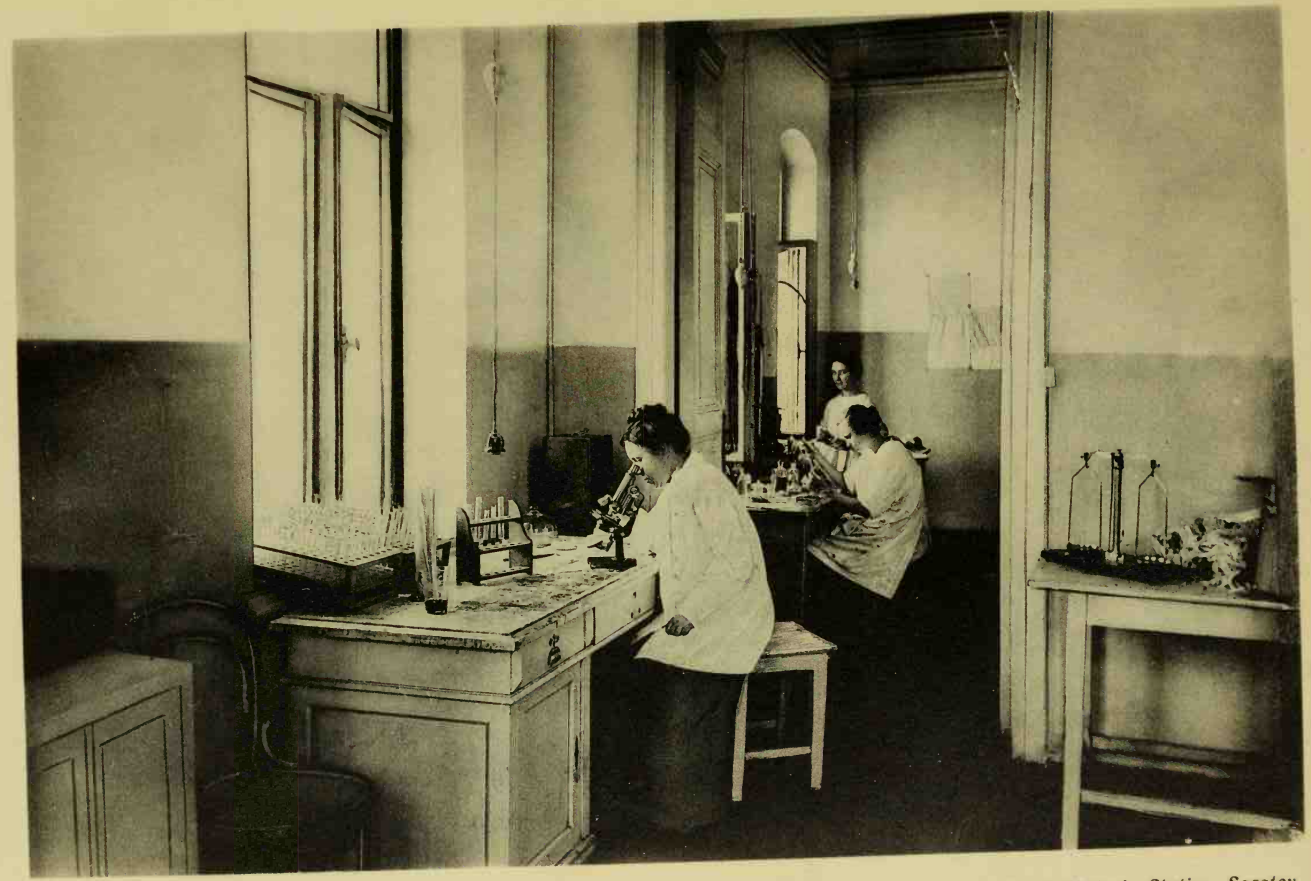

Plate X

RUSSIA

Malaria Station, Saratov. Laboratory

Photo Malaria Station, Saratov

Plate XI

RUSSIA

Malaria Station, Saratov. Injecton of qiuinine

Photo Malaria Station, Saratov

Plate XII

RUSSIA

Photo Institute for Tropical Diseases, Moscow

Institute for Tropical Diseases, Moscow. Propaganda Museum

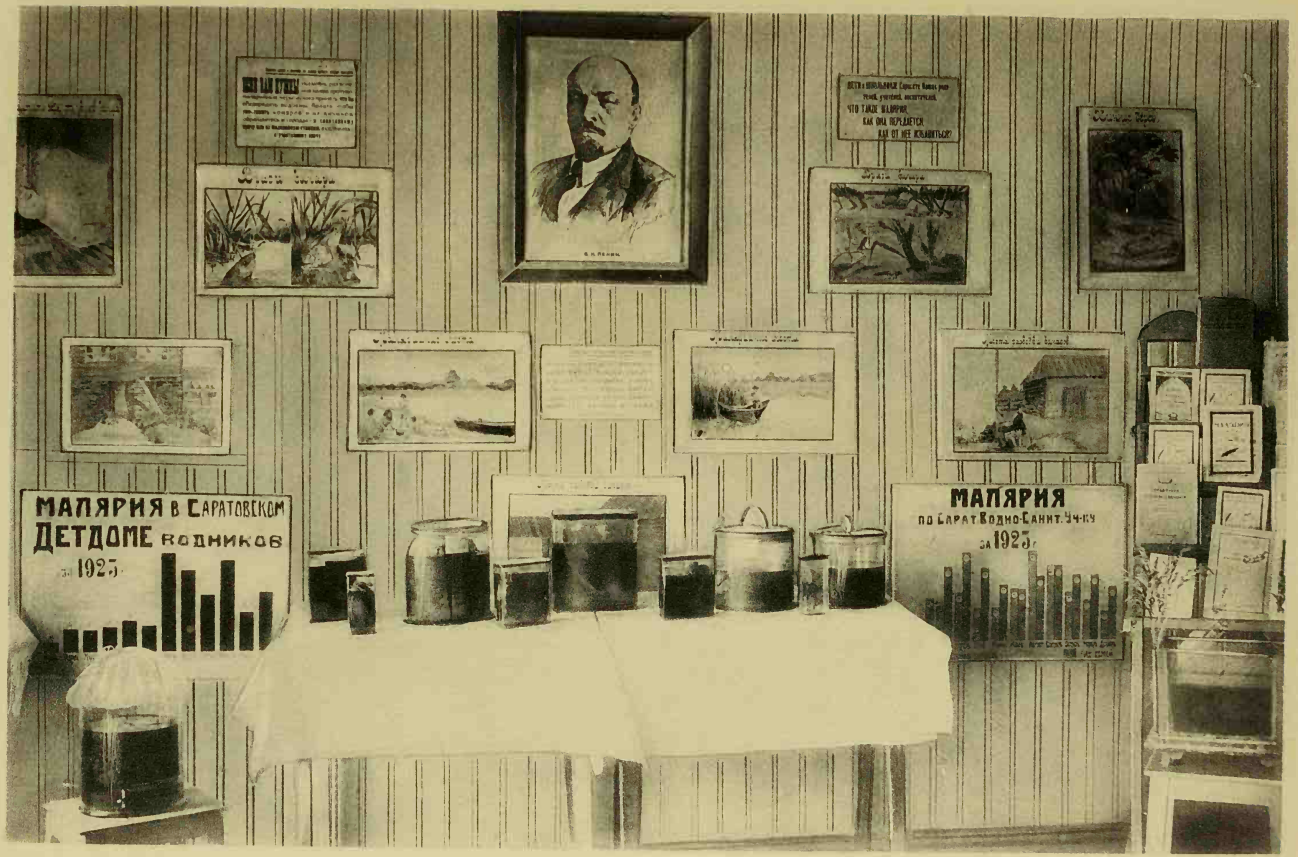

Plate XIII

RUSSIA

Malaria exhibition in railway carriage, Saratov

Photo Malaria Station, Saratov

Erivan, Tiflis and Bokhara, which are chiefly for scientific research, training of doctors and auxiliary staff for combating malaria, but also do service as malaria stations (with clinic and policlinic).

b. Sections for malaria in 13 existing bacteriological laboratories (chiefly investigation).

c. 113 malaria stations (Plates X & XI) (in 1923, this year there are more) distributed unequally over the territory of the Union, for instance in European Russia (that is, old European Russia without the border States Ukraine, White Russia and the Caucasus) 52, Ukraine alone 13 (now 47), Siberia with Central Asia 10, etc. Each station has a policlinic, a laboratory and a propaganda museum. (Plate XII). To each station there are attached 1 to 2 (sometimes more) doctors, 1 to 2 assistants and minor staff. In addition to examination and treatment of the sufferers, who attend or are sought out (see above) the station engages in the fight against larvae and adult anopheles, and chiefly in propaganda. (Plate XIII). Sometimes a part of the country is studied and assisted by means of "detachments". Most stations were only opened in the course of 1922 or 1923.

The costs (the amount or estimate of which are not known to me) are borne:

a. By the Commissariat of Public Health of the Union, namely for: 1. the equipment of malaria stations and payment of their principal staff; 2. that portion of the quinine which is distributed free of charge.

b. By the local services in respect of: 1. the maintenance of the stations; 2. the remainder of the quinine; 3. the "small sanitation".

In *Bulgaria* also there is a separate malaria service, regulated by the law of the 13th April 1919. The direction is in the hands of the "Malaria Inspectorate" standing under the General Director of Public Health in the Home Ministry, consisting of a doctor, a civil-engineer and a zoologist. Its sphere of operation consists of the districts declared infected with malaria, in each of which 40 to 60 villages are situate. In each district there is a medical inspector with an office and a laboratory for blood examination, with one or more miscroscopists. In each village there is a quinine distributor, who also takes blood-slides (a so-called "Feldscher", something like the Dutch East Indies native-assistant, but not on a same level of development) and notifies the malaria cases; also the necessary drivers and labourers (for the sanitation works) and voluntary assistance, at 10 levs per day, such as schoolmasters, priests and students.

The task of the medical inspector is to examine the blood slides coming in, to maintain supervision over the big works of reclamation,

which are paid for out of the funds at the disposal of the Malaria Inspectorate, and the small works of reclamation, which are paid for by the landowners. He also maintains supervision over the distribution of quinine (free of charge to everyone), over the fixing of gauze protection (at the expense of the Inspectorate, communes or employers), and the construction of houses (only permitted after the opinion of the Inspectorate is sought; within villages and town districts only after permission of the body in question is secured).

The similarity with the Serbian system and the contrast with the Russian system therefore lies in the fact that the medical inspector maintains some connection with all the villages in his district, though this connection in Serbia is closer.

The expenses for malaria fighting, in so far as they are borne by the State, are covered by the "malaria fund" under the administration of the Inspectorate. It now amounts to 7 million levs and consists of the yield of a capital of 3 million and a yearly contribution of 50,000 levs, both supplied by the State. Also 5% of the communal and 10% of the departmental revenues in the regions declared infected with malaria, all revenues from reclaimed land for 15 years (save in so far as carried out by private persons, in which case they pass to the latter) and the proceeds of fines imposed in respect of offences against malaria legislation. For the rest, this does not quite correctly reproduce the expenses, because the civil-engineer of the inspectorate had an extraordinary credit of 11 millions for the purpose of executing works outside the malaria fund. Moreover the expenses of the quinine monopoly (this year 20 million levs) are not included.

In *Greek Macedonia*, the combating of malaria which is there carried out chiefly by means of medicaments coincides with the general medical provision for the refugees in the towns and of the entire population in the country, and therefore presents nothing remarkable from the point of view of malariology. Provision is made however for future requirements by training the auxilliary staff for the larval, mosquito- and quinine-squads in two schools at Salonika and at Athens. Each squad, of which there are twenty intended for Macedonia, and ten already in operation, consists of a chief (student of medicine), who earns 50 drachmas, a male nurse earning 40 drachmas, and 5 to 10 labourers each of whom earn 30 drachmas per day. Administratively they are under the departmental physician in whose area they work and they are supervised for the entire country by 3 medical inspectors. Their task is the seeking out and treatment of sufferers, in summer, the execution of small sanitation work, in winter, the fumigation of houses. In one district we saw 2 squads to 40.000 inhabitants in

150 villages. Large scale sanitation is to be left to private initiative.

This scarcely organised service of malaria fighting is under a commission of 4 delegates from 4 Ministries (Health, Public Works, Agriculture and Finance) and is under the supervision of the Ministry of of Public Health. The budget is 4 million drachmas (30 had been applied for).

In *Roumania* there has been only local malaria control hitherto and exclusively by medicaments. It is not intended either to establish a special service, the departmental doctors who now have the management remain the officers who execute the central orders (with the country doctors under them, who are here mostly State officials). In order however to gain a better insight into the spread of malaria, the so-called "flying brigades" will be organised, assisted by 11 stationary laboratories (including the University laboratories of Bucharest, Jassy and Cluj), and 12 flying laboratories. Each flying brigade consists of 1 doctor and 4 students of medicine in their last year of study (it is intended to compel all students of medicine, after completion of their studies to go through one year's practical work in one of the branches of the State service of Public Health). Their task consists in seeking out sufferers, making blood slides, registering the splenic index of children up to their 16th year, collecting of entomological material and particulars regarding: the breeding places of anopheles, their occurrence in houses, the occurrence of malaria houses, meteorology and geology of the infected areas, economic conditions of the population and number of inhabitants. The area of each brigade comprises about 2000 inhabitants. If this plan can be carried out Roumania may come to be one of the best informed countries in the world in the matter of malaria statistics.

In *Italy*, malaria fighting is, as regards the State, not incorporated into one service and even belongs to different Ministries, for instance, as regards drainage, it belongs to the Ministry of Public Works, and as regards the quinine monopoly, the Ministry of Finance. In addition too, the State leaves a great deal to private and communal initiative, so that considerable decentralisation occurs. In order therefore to avoid excessive detail here, I must keep very much to the surface of things.

The State, by means of the quinine monopoly and the supplying of quinine free of charge or at a low price, is immediately engaged in fighting malaria. It extends this influence by legal enactments, which compel doctors to notify malaria cases and, under certain circumstances, forces communes or private employers in the regions declared to be malaria infested, to distribute quinine free of charge. A prominent

point of view in this connection is that malaria is considered as a professional disease. In this matter the State itself does the following:

1. It promotes the judicious use of quinine by means of the existing medical organisation (provincial and sub-prefectural doctors, "medici condotti", in the communes, with their hospitals), by posts for quinine distribution along the roads and by 1200 policlinics for malaria sufferers. (Plate XIV).

2. It undertakes the care of the personnel of the State railways and the army, not only as regards quinine supply, but also by gauze protection and measures against breeding places, both of which, or the latter alone, are, under certain circumstances (rice growing, retting ponds, and in the new law, all "bonifications") made obligatory on others.

3. It provides for the training of the necessary auxiliary staff in fighting malaria, by the school at Nettuno, where every year 5 to 6 courses of 2 to 3 weeks are held. The establishment costs 40,000 Lire and maintenance costs 10,000. The higher staff however do the work as a by-employment and resides at Rome; the whole is accommodated in a portion of a military building.

4. It assists, by means of subsidies granted under certain conditions, in rendering suitable for agriculture and residence, lakes, lagoons and marshes, and works such as afforestation of mountains, regulation of watercourses, etc., which may be of service for the same purpose. In part, it carries out these works itself. I have already pointed out that it may seem to us rather strange that this should be classified in particular under the fighting of malaria, but that this standpoint is quite defensible if only it is not considered as an anti-larval measure.

Of the special bodies to which the State transfers a portion of its task I may mention:

A. In the province of Venetia.

1. The "Magistrato per le acque", which supplies directive instructions for the reclamation work carried out by private bodies (the "consorzios").

2. The "Istituto autonomo per la lotta contra la malaria". The object of this body is malaria fighting by drugs, with 42 "ambulances" (with doctor, policlinic, sometimes a small sick ward), 22 "dispensaries" (for quinine distribution), 2 stations for malaria radio-therapy and 3 childrens' sanatoria in the mountains, for children with chronic malaria. Also combating by means of drainage and measures against larvae and, finally, by improvement of the water supply in the existing reclaimed lands. I do not know how large the entire population is among which this body works; in the environs of S'Dona di Piave there were

Plate XIV

ITALY *Photo Italian Red Cross, Malaria Control Department*

Treatment and prophylaxy at home by the Red Cross, Pontine marshes

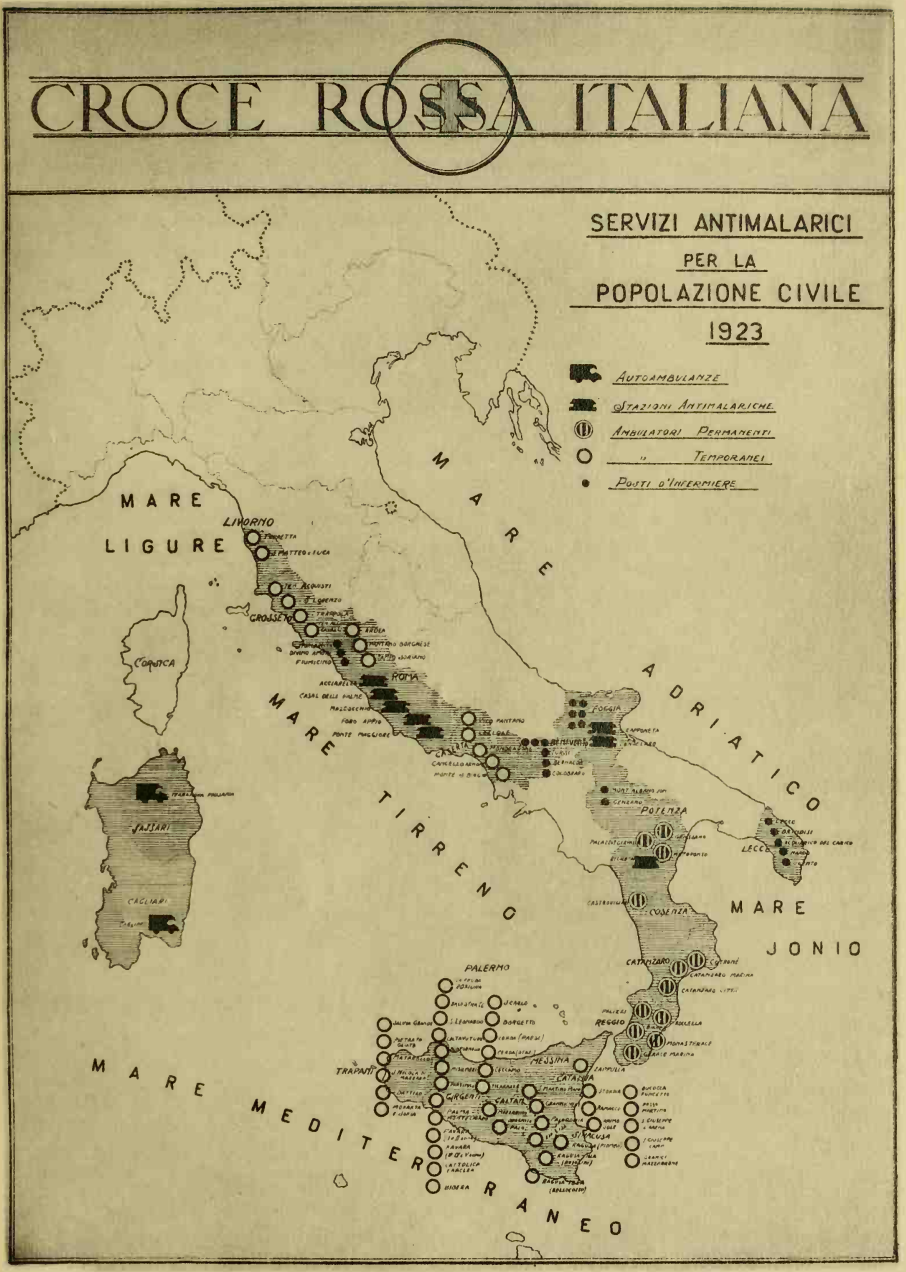

Photo Italian Red Cross, Malaria Control Department

Plate XV ITALY Page 35

Survey map of the Anti-malaria service of the Red Cross, Pontine Marshes

7 ambulances with 4 doctors, 1 student and 9 male nurses to 11,700 inhabitants. But this was a severely infested region.

B. The Italian Red Cross works in various parts of Italy, (Plate XV) but above all in the Pontine Marshes, Sicily and Sardinia. The chief work again is the distribution of quinine under medical supervision. For that purpose they have:

1. The "ambulances" with dispensary, policlinic, small sick ward for severe cases and a staff consisting of a doctor, who gives his entire time (and receives 1200 Lire per month), 3 male nurses, 1 female nurse, 1 driver, 1 cart, 2 horses and the necessary drugs. The costs are 6,000 Lire per month. There are 5 of them in the Pontine Marshes, each of which also has the medical charge of 3 schools for their account in which they co-operate with the "Liga contra l'analfabetismo" and each covers an area with a radius of 40 kilometres, which the doctor traverses entirely in 4 to 5 days.

2. The "ambulatory" service in the regions where there are more doctors, of whom one at a remuneration of 300 to 400 Lire per month gives a part of his time to the maintenance of a policlinic. The only whole time staff is a district nurse and a housekeeper; costs 2000 Lire per month. There are about 80 of these in various parts of the country.

3. The "motor ambulances", in principle the same as the ambulances, but everything can be loaded on a motor-car and can therefore be readily conveyed where most required. There are 2 in Sardinia. They cost 50.000 Lire per annum.

4. The Childrens' Sanatoria, of which there are 2 (Pontine Marshes).

5. A station for radio-therapy of malaria (Pais system) in the mountains (Sezze) adjoining the same marshes.

In all there are thus treated per year 60.000 malaria sufferers with 1000 kg. of quinine (17 grams per patient: compare with this the 90 grams per head of the population used in Greece for prophylaxis alone).

C. The Commune of Rome has, in the Agro Romano, 33 "sanitary stations" to which a doctor is attached, who maintains a regular policlinic and together with the district nurses attached to the station, travels through the environs on horse, bicycle or motor-cycle and also visits schools. There is telephonic communication with the Ufficio d'Igiene (for speedy help), a small sick ward, an establishment for urgent surgical measures and a dispensary. Each station can deal with fully 2000 inhabitants. In addition to this there are 14 "punti aussiliari di profilassi", each with a "profilassator", a quinine distributor and a number of "signalatori" for seeking out sufferers who do not come themselves for treatment. Finally, there are stations in the moun-

tains in the environs for treatment of the mountain dwellers, who work in the plains in the summer and contract malaria there. For children suffering from chronic malaria there is a sanatorium in Rome. In some stations (particularly Ostia) a good deal is done for the destruction of larvae and mosquitoes. This entire organisation costs every year about 1 million Lire (400.000 for quinine and 600.000 for the stations).

As regards costs, it may further be said, that the subsidies to various bodies which co-operate in the fight against malaria amount annually to an average of 2.5 million Lire; the cost and subsidies for great and small "bonifications" are about 16 million (in 1900 to 1920; before that time only 4 million). The net proceeds from the quinine monopoly on the other hand, amount to about 1 million per year.

3. *Extent of malaria.*

Most communications agreed in this that, towards the end of the war, malaria was in process of increasing and in 1922 or 1923 had reached its climax (except in the Ukraine where it was greater in 1924), and was now declining, or at least bore a less serious character. As to a decline there can only be a question when we know how much malaria there was and how much there is now. And as we always had to take as our basis the results of examination of patients who reported themselves to malaria stations (the particulars prior to 1922 were based on local data which could not be checked in any way) we really do not know anywhere exactly how much malaria there was, and, only as regards a few places, how much there is now.

It would take me too far to discuss here the various defects inherent in the statistics received by us. They did not allow of forming a just idea of the influence of the various measures on the course of the epidemic, the less so as an epidemic recrudescence was in question of the everywhere endemic malaria; and experience shows that such recrudescences again disappear after a time. The measures taken may promote such disappearance, they do not cause it.

In *Dalmatia* the organisation was such as to enable the epidemic doctors to come into contact with the entire population. Yet the malaria position was not well known, because at the stations only that portion of the population which attended was examined, which caused the figures to turn out too high. Only in Marina, Trogir and Metcovic was a great portion of the population examined. In Marina (Karst area) the percentage of parasite-carriers (subsequently referred to as P. I.) fell from 41 per cent. in 1922, to 5 per cent. in 1923 and to a very few in 1924 (up to 1st June). In Trogir (Karst area) the figures

Plate XVI

DALMATIA

Splenomegalia in man, shown by stripes

Photo Dr. Svarcic, Trogir

were respectively 15 per cent. — 12 per cent. — very few. In Metcovic (inundation territory) the splenic-index (referred to hereafter as S. I.) was 80 per cent. in 1922 in children, 68 per cent. in 1923 in children and adults, and 50 per cent. in children in 1924. (Plate XVI). During our visit there was a great deal of malaria in some regions of the barren Karst; at Vrana we found in the school children an S. I. = 95 per cent.; at Konjovrate = 65 per cent.

In *Croatia* (Island of Krk) the S. I. in 1923 was 30 to 35 per cent., P. I. = 2 to 11 per cent.; in 1924 (till the 1st of April) 18 per cent. and 1.5 to 4 per cent.; on our visit the S. I. in children was nil.

In *Serbian Macedonia* the service of the stations had been begun too recently to allow of observing any changes. Only at Duschanowatz near Skoplje was the S. I. in children in 1922, 35 per cent., and is now 19 per cent. A figure agreeing with the latter was shown at Prizren. Higher figures were shown however in the inundation territory round Struga (43 per cent.) and the district of Stip (42 per cent.).

In *Greek Macedonia*, after the importation of 300,000 refugees in 1915 a recrudescence of malaria occurred, which attained its maximum in 1916 and which was repeated in 1923, after the influx had begun again in 1922. Nothing is known of malaria statistics among the native population, and I have already mentioned the uncertainty in this respect. The death-rate from malaria (in contrast with almost all other places which we visited) was high; 70 per thousand of all inhabitants of the Camp at Toemba near Salonika, 50 to 70 per thousand in the district of Langada, 18 per thousand in Yanitza and 6 per thousand in Salonika. The S. I. among the refugees was 57 per cent. at Yanitza and among those in the Struma Valley 20 per cent. (children).

In *Bulgaria* the notification of malaria is obligatory on heads of families, priests and teachers and is then checked by the before mentioned "Feldscher". In addition to this, in 1922, a spleen examination for purposes of information took place, and it will surprise no one that the two did not agree with each other, so that a good deal of malaria was reported from districts with low splenic-index and vice versa. We ourselves found in the Maritza valley an S. I. of 25 to 32 per cent. (in 1922 it was 47 per cent.), and near Burgas 52 per cent. (all in children). The mortality in consequence of malaria is given for 1921-1923 as 0.5 to 0.9 per thousand (general death rate 19 to 30 per thousand).

In *Roumania* statistical enquiry is still to begin. There are only known some figures regarding the number of malaria patients in hospitals. We found there an S. I. of 13 to 38 per cent., only once (village in the Jiul Valley) of 66 per cent.

In *Russia* there exist since 1887 particulars regarding the number of malaria cases (strangely enough not covering the mortality from malaria) which showed maximums in 1894 (272 per 10,000), 1897 (269 per 10,000), 1899 (282 per 10,000), 1903 (271 per 10,000), 1908-1910 (229 per 10.000), 1923 (440 per 10,000). How these figures were and are collected and what value they possess we were not told, even after specially asking for it. Certainly in some of the places, perhaps in most, the ubiquitous "Feldscher", is responsible for them. Therefore these figures are not considered trustworthy — not even after the introduction of compulsory notification in 1921, but it is considered that they may be serviceable if multiplied by a factor varying from 2 to 5, not taking into consideration that the data, just as in Bulgaria, may be too high. In these circumstances it does not come within my intention to discuss here the various conclusions made on the basis of these figures (for instance, the influence of crop failure on malaria).

The data of the malaria stations in themselves are correct, but cannot be used statistically because they represent the examination of an unknown portion of the sufferers of a population of unknown size. Furthermore, the number of sufferers who report themselves depends on the stock of quinine at the station. If the latter is large more patients appear. Therefore it is by no means certain, for instance, in 1924, that in the Ukraine there was more malaria than in 1923, because there was much more quinine available.

The examination of the population is mostly limited to the inhabitants of childrens' homes and factory workers in the towns. The former mostly emanate from quite a different part of the country (in Kharkov for instance, Tartar children from the Volga). As these groups after being examined were thoroughly treated with quinine (as is indeed right) they are not serviceable for any later comparison except in order to show the efficiency of the treatment. For the purpose of determining the extent of the malaria among the population therefore, only those investigations of certain "detachments" who carried out spleen and blood tests among a large part of the inhabitants of certain villages in the Don territory and in the Steppes to the East of the Volga are of value. In the last named territory (Novo Uzensk) there were found 65 per cent. of malaria sufferers in the autumn of 1922 and 42 per cent. in May 1923 (in two different seasons, therefore not comparable). In the course of time such investigations may furnish serviceable results.

During our stay we seldom found very extensive malaria. Considering the population proper alone, we found in the Ukraine an S. I. of 30 per cent. and also in the Don territory (except in one village —

69 per cent.), in the Volga territory 13 to 36 per cent. (once 66 per cent.).

In *Italy*, in spite of the compulsory notification of malaria, little value is attached to these statistics, except to those of the Red Cross in the Pontine Marshes and the Commune of Rome in the Agro Romano. I make no mention here of the army and the employees of the State railways, because these form a non natural and a changing population. Nor, for the same reasons the population of Fiumicino, chosen by *Grassi* as a subject of study.

In the Pontine Marshes the percentage of malaria sufferers fell from 7 per cent. in 1909 to 4 per cent. in 1914, then rose in 1916 to 14 per cent., in 1918 again to 13 per cent. and fell to 11 per cent. in 1921. In the Agro Romano these figures were : 31 per cent. in 1900, 20 per cent. in 1901 and 1902, 11 per cent. in 1903, 4 per cent. in 1909, 6 per cent. in 1914, 11 per cent. in 1918 and 4 per cent. in 1921.

As is well known great importance is attached in Italy to the mortality figures due to malaria. They dropped from 0.7 per thousand in 1887 to 0.06 per thousand in 1923, with a rise to 0,3 per thousand in 1918. Before 1900 this decline alternated with recrudescences (continually decreasing). After that time the decline runs regularly, except for the war disturbance.

4. Character of the malaria.

Quite generally it was said, that before the war there was much less tropical malaria than after it. This was asserted particularly in Greece, where the refugees were said to have imported it. In other quarters this again was contradicted and my impression is that nothing is really known concerning it.

All three forms of parasites occur in the countries visited by us. The tertian is mostly found in May, only in some places in Serbia it was thought that two tertian climaxes were observed, one in May-June, due to relapses, the other in August or later, due to primary cases. The tropical is found in August-October, the quartan in autumn. In Saratov it was thought that the tertian climax in May was due to primary cases. As this falls within a time when there are but few anopheles, these cases (just as with us) are attributed to infections in the previous season or in the winter. Similar observations were made also elsewhere. For the quartan likewise, a long period of latency is assumed, because it breaks out at a time when there are no more anopheles.

The relation between the number of carriers of the different kinds of parasites will therefore no doubt vary according as the investigation is made in spring or autumn. Thus, in Novo-Uzensk in May 85 per

cent. of the carriers were found with tertian, 15 per cent. with tropical; in the autumn these figures were 15 per cent. and 87 per cent., almost the reverse. As sufficient attention is not always paid to this, the figures are not entirely comparable with each other for the different countries.

In *Dalmatia* there was, for the entire year 38 per cent. tropical, 43 per cent. tertian and 26 per cent. quartan.

In *Serbian Macedonia* there was found 37 to 45 per cent. tropical, but in *Slovenia* the tertian predominated (81 per cent.), while the tropical, in addition, was so benign that it was thought to be a race differing from the Macedonian. In *Bulgaria* there was somewhat less tropical (24 per cent.), still less in the *Ukraine* (6 to 11 per cent.), but further south, in the Rostoff region, again much more (25 to 52 per cent.), also on the southern Volga (51 per cent.). In the environs of Moscow and Nijni Novgorod, the tropical figure was least (2 to 5 per cent.).

The mortality from malaria was, generally speaking, low, even in the so severely visited Volga territory (0.4 to 0.5 per cent., 3.5 per cent. at the most). An exception is constituted only by the refugees in *Greek Macedonia*; the refugees in the Camp at Toemba near Salonika and the district of Langada (mortality figures on page 37).

Blackwater fever occurred in some parts of *Dalmatia*, *Serbia* and *Greek Macedonia*. I may refrain from a summing up of other phenomena, as it was but too often not clear whether or not there was confusion with another disease. This was positively denied, on the basis of bacteriological and protozoological results, for dysenteric forms of malaria.

Interesting were the communications about congenital malaria, ascertained parasitologically shortly after birth. In Skradin *(Dalmatia)* in the course of 2 years, 40 of these cases were observed; the parasites were found 1 to 5 days after birth. At Persianovka (Don territory) in 8 cases the parasites were found 2 hours after birth; at Zarizyn (Volga) in 2 cases immediately after birth in mother and child and in the blood of the umbilical cord.

Phenomena of "immunity" against malaria would be of particular interest in the infested regions, because all of them have seasonal malaria which is considered as less suitable for creating a condition of "immunity" than continuous malaria, as is sometimes found in the tropics.

In *Serbian Macedonia* where, here and there, many settlers are found from regions infested little or not at all with malaria, the impression was that they have to suffer more from malaria than the original population, at any rate during the first three years. Of course

so vague a statement means very little. More interesting is what we observed in *Greek Macedonia* (Yanitza) where, among children of the original population, we found no enlargement of the spleen, and among those of the refugees, a splenic index of 57 per cent. But, the refugees were perhaps more exposed to infection than the old inhabitants. In Kazan, finally, an examination of children and adults yielded the following results:

		Spleen index	Parasite index
Children	0—13 years,	49 per cent.	52—47 per cent.
Labourers ..... below	20 „	36 „ „	27 „ „
„ .... „	20—29 „	29 „ „	16 „ „
„ .... „	30—39 „	27 „ „	4 „ „
„ .... „	40—52 „	21—22 „ „	5 „ „

which certainly points in the direction of an immunity arising in the course of the years.

None of these data are however sufficient to decide the point.

5. *The use of quinine in the fight against malaria.*

I am of opinion that since the war, the value of quinine has been estimated higher than previously, because there was a dearth of it. I have already reported this in connection with Russia, but almost everywhere the lack of quinine was given us as being one of the causes of the sudden recrudescence of malaria.

Too much was formerly expected from quinine: entire disinfection of the blood and consequent stoppage of the malaria. When it was found that it could not do this, many thought it good enough for individual work, but not for work on a large scale. Now also we frequently encountered the opinion that the struggle against malaria is only effective when it is a struggle against the mosquito; quinine treatment is only patchwork. This is really still the official opinion everywhere, and even not wholly unknown in Italy. The above mentioned valuation of quinine is indeed only a half-conscious one. In practice however, the actual fight mostly comes to quinine treatment.

This is quite consciously applied in *Roumania*, where all anti-larval work is abandoned. As early as 1906—1912 in a series of villages, with a maximum of 125,000 inhabitants, regular quinine prophylaxy and treatment was applied to a part of the population (the rest serving for control), with continuous control of the diagnosis by blood test. Good results were obtained, though nature helped powerfully, as is shown by the reduction of malaria in the entire country. The attempt is now made to get rid of the source of infection by disinfecting all sufferers of the previous year by a daily dose of 2 grams of quinine

for 10 days between the 1st April and 1st July (before the 1st July it is held that no new infections occur). If necessary this is continued by 1 gram of quinine twice a week or 0,4 per day. Distribution, in default of doctors, is effected by "sanitary agents" (= "Feldschers").

The stock of quinine in Roumania is 24,000 Kg. The population knows its value; on market days the farmers pay 10 lei (about twopence) for it. In 1922, 1532 kilos of quinine were consumed, in 1923, 2515 kg. and in the first half year of 1924, 1534 kg.

In *Bulgaria* there is a quinine monopoly. Except for paupers, quinine is only available to all free of charge in those districts which are declared to be infected with malaria. The State now distributes annually 6000 kgs. of quinine of the value of 20 million levs (about £ 5.12.— per kg.). Prophylaxy is limited to the most severely smitten regions. Among the population after treatment is mostly inefficient. Distribution is effected through the "Feldschers". In the district of Philippopel, to each malaria sufferer there was not more than 3.5 grams of quinine per year.

In *Serbia* the most important work of the epidemic doctors is the distribution of quinine (see: Organisation). Whether the reduction of the malaria in Marina and Trogir in 1923 is to be explained by quinine treatment, or by the anti-larval measures likewise carried out there, cannot of course be ascertained. Elsewhere work had been begun too recently to allow of judging results. Where feasible the fight by means of medicines was assisted by improvement in feeding of the population (distribution of flour: the German "bread control" of malaria).

Greek Macedonia was distinguished by very large quinine doses. In the Harmakioi camp, for instance, there was given as a curative agent daily for 2 to 3 days, 2 grams of quinine in urethane, intragluteal, continuing it per os. In Kalamaria there was given as a prophylactic, 1 gram of quinine 5 days per week. In spite of those large doses (which may even go up to 3 to 4 grams), cases of malaria are complained of which are quite refractory, even after intermittent treatment continued for weeks! Owing to the general decline of malaria in 1924 the results, to be attributed to quinine treatment in particular, could not be observed.Judging from the unusually high mortality from malaria in the Camp of Toemba the effect seems at times to have been exceedingly slight. In the malaria areas the entire population receives per day 0.5 gram of quinine from May to October, which makes 90 grams per head. The supply is for 8 to 10 days at a time. Distribution is effected through local commissions, on which the schoolmaster, priest, and other notables sit.

As regards *Italy*, I need only point to the generally known mortal-

ity statistics, the favourable outcome of which is attributed in the first place to the quinine laws.

Perhaps to some the statistics already mentioned, from the Agro Romano and the Pontine Marshes are of more value. The former show a heavy decline in the number of malaria cases, while the latter indicate little permanent improvement. In the former, quinine treatment was applied and the country drained and latterly powerful measures have been taken against larvae (but the improvement dates from long before this latter measure). In the Pontine Marshes quinine treatment is almost the only thing: the population really lives in the mountains and comes down from September to June to look after livestock, burn charcoal and, to a small extent, to do agricultural and garden work. They live in huts which are far inferior to the dwellings of our Javanese, although they are often quite well off from a money point of view. These wanderers also come and look for work in the Agro, but there is also a fixed population. Which of these factors results in the success being so much greater in the Agro than in the Pontine Marshes I do not venture to decide.The human factor too appears to have a great influence on this success.

The State supplies annually 60.000 kg. of quinine. I have already spoken (page 35) about the quinine consumption of the Italian Red Cross.

We saw perhaps most clearly in *Russia* the influence of quinine, or at any rate heard of it. I do not mean the demonstration which this country provides as to how an almost pure tertian epidemic looks when no quinine is available (page 28), but rather the positive results secured there in childrens' homes and labourers groups. Owing to the peculiar system prevailing control groups were frequently to be found and would be even more numerous if we had been able to see a little more of the agricultural population. Thus we found the splenic index of the children in childrens' homes and labourers colonies in various places to be 2.5 to 9 per cent., for other children 30 to 69 per cent. The former were treated with quinine, both as a curative and prophylactic treatment and were presumably also better fed, clothed and housed.

The most important outcome in the department of quinine treatment of malaria is no doubt secured in the peat areas of the Governments of Moscow and Nishegorod, which I already mentioned on page 28.

The method of quinine administration in Russia shows, here and there, a curious feature. Thus, in the Ukraine, it is done by the *Roubashkine* method, viz. sub-cutaneous injections of 0.5 to 1 gram of

quinine hydrochloride per day in all cases, for the after treatment also, and in combination with antipyrine and iodine, or with methylene blue. This is done here because it is thought that less relapses thus occur, (a thing which, for that matter, is contradicted by the experience in Rostoff, at least as regards the long date relapses), but in Tsaratsin, where injections are also constantly made, this is done in order to manage with a less quantity of quinine. Against the habit, known in Russia likewise, of giving quinine for a long time successively in order to fight relapses, objection was raised in Rostoff. The after treatment consists in a dose of 1.5 gram of quinine 2 days out of every 8. If those 2 days are increased to 6 it makes no difference as regards the likelihood of relapse.

As regards the quantity of available quinine salts, this amounted in Russia in 1922 to 8,000 kg. (2.5 grams per patient per year), in 1923, 12,000 kg. (2 grams ditto), in 1924, 60,000 kg. (10 grams ditto). It is believed that there are required 240,000 kg. per year, (i,e., 20 grams per patient per year, this number being estimated in 1925 at 12 million). A part of the quinine is supplied gratis, another portion is bought by local organisations for resale (in the Ukraine, for instance, in 1924, 2,840 kg. of the former and 2,000 kg. of the latter).

6. *Measures against larvae and full grown anopheles.*

Although it is no new observation, we are nevertheless each time struck by the fact that there is frequently so little connection between the observable density of the anopheles population and the amount of malaria in a place, even when the species is always in question (as was the case in our journey, namely: exclusively with *A. maculipennis*, apart from *A. elutus*, in addition to the first mentioned, at Metcovic in *Dalmatia*).

We found a large number of anopheles (100 to 260) per house to be accompanied by a high (69 per cent.) and medium (36 to 28 per cent.) splenic index; a low number of the first named (less than 10 per house) we found in places with very high (83 to 95 per cent.), high (66 per cent.), medium (30 per cent.) and low (10 to 14 per cent.) splenic index. This fact can be explained in various ways: *Grassi* says that this want of agreement is so great and that among the few anopheles in a heavily infested territory, infected ones are so seldom encountered that he must suppose that they are able to convey the malaria direct (that is without sexual development of the parasite). For my part, I assume that in principle a relatively small number of anopheles are required (frequently far less than there really are) in order to maintain the level of malaria anywhere, and that once this has been reached,

it depends on entirely different factors (the nature of which we can merely guess at) whether the malaria will continue, will increase or decline. This hypothesis (which in turn contains nothing new) would explain why, in general, and again on this journey, so little was observed of the useful effect of the many measures for destruction of larvae and mosquitoes, which we saw or heard of. To this however it must at once be added that, in many cases, the nature of the statistics did not allow of ascertaining a good result which may have been obtained, and in so far as concerns the measures against the larvae, the rich catches of full grown mosquitoes in the houses or stables round about, but too frequently rendered clear the inadequacy of these measures.

I cannot here enter upon a description of the breeding places and the catches of mosquitoes in houses and stables which we found and performed, nor sum up the measures against larvae and adult insects, which were shown us either in reality or on paper. Suffice it here to remark that the only anti-larval measure which really promised anything good was that in the Karst territory against the lokvas (see page 26) and that, not because of the perfection of the method, but owing to the peculiar nature of the land.

One feels convinced that to fight malaria exclusively by means of the fullest possible tracing and treatment of the sufferers and healthy parasite carriers, would be equivalent to fighting typhus on the same basis (which would therefore go to benefit, not the sufferers alone but, owing to reduction of the likelihood of infection, the public health generally) without the other measures usually considered necessary. Such combating of malaria is therefore incomplete and also disregards all discoveries made in this department since 1898. The measures which must be taken however are so expensive (or to express it better, precisely the so-called "small measures") if they are to do any good, and they are of so little general use, are so specialised (at least if one excludes the big drainages, which are not generally included among the measures against malaria in its proper sense) that they cannot be compared, for instance, with improvement of the drinking water — supply or the removing of faeces.

Thus there is a certain tendency to be somewhat more careful than previously in measures against mosquitoes, and above all against larvae, in fighting malaria. They are no longer included without any motive in every anti-malaria programme before it has been thoroughly ascertained whether they are capable of fulfilment. And finally, to have the courage *not* to take such measures, if not found to be capable of practical performance or if there is no reasonable chance of success. How far this tendency, which was certainly not to be found in any

of the countries visited by us as clearly as here, except perhaps in Italy, will become the prevalent opinion, cannot yet be stated.

Next to this negative there is something positive: the place par excellence where infection from *A. maculipennis* occurs is the dwellinghouse; the likelihood of malaria infection is greater:

1. In proportion as there are more people living it it;
2. The longer the house offers the anopheles the opportunity of remaining undisturbed.

The chief point therefore is not how many anopheles there are in a country, nor yet how many make their way at a given moment into a house, but how many remain there, and this number depends more on the nature of the house than on the first mentioned factor.

As regards the first point, it became clearly evident in the still uncompleted lands reclaimed in the Piave territory (province of Venetia) where, among the labourers residing in sheds, much more malaria occurred than in the lands long since reclaimed. Yet the number of anopheles found in those two territories in houses or stables shewed no appreciable difference. In this connection my mind goes back to the barrack camps of the refugees around Salonika, which, owing to the density of their aggregation, for that reason alone, most certainly contributed to the great extension of malaria. This is entirely in agreement therefore with another phenomenon observed in our country, namely: that in houses resided in by big families there are often found more infected anopheles than in those with small families. Under these circumstances (labourers barracks) it might be imagined that gauze protection acquires special value, as we saw it applied in the peat grounds of Chaturka with good results (i.e. many anopheles in the pigsty, adjoining, but none in the barracks).

The second point can be understood but is still no more than a hypothesis, as it can only be proved by finding infected mosquitoes in some kinds of houses and their absence or scarcety in others. Experience regarding the occurrence of "malaria houses" does indeed point to the suggestion that one house offers more chance of infection than another, but we have not yet much positive knowledge with regard to such chances and in relation to the character and installation of the house.

Notwithstanding these lacunae, the view is thus arrived at — and in this connection, the name of Colonel *James* must be mentioned in the first place — of considering the malaria question as a housing question and attaching primary importance to the removal of anopheles in dwellings, not with the object of reducing the number of mosquitoes, but because in dwellings there is the greater chance of

catching infected mosquitoes. As is well known, such measures have been applied in and around Amsterdam on the basis of considerations similar in principle. The same applies to India (*Schüffner's* malaria combating in Great Mandailing). Needless to say, they are only of value if the malaria carrier is a mosquito which is in the habit of sucking blood in the house and (under favourable circumstances) remaining therein for a long time.

7. *Lessons to be drawn for Holland.*

There is nothing really new to us to be concluded from the foregoing. Yet special emphasis must once more be laid on certain points:

In the first place this: that it is unjust towards Dutch doctors to say that in this country nothing is done against malaria, as was said in 1920 and before, prior to the commencement of the great mosquito campaigns. What other countries endeavour to introduce with difficulty, what they point to with pride: an organisation to bring quinine really within the reach of all, that organisation we possess thanks to the co-operation of doctors, medical State supervision, sick funds and the wholesale quinine trade. Thanks to that co-operation a severe epidemic such as that of 1918—1922 (think for instance of Nieuwendam: 17 per cent. of malaria without the relapses of the same year), passed over the population of North-Holland without occasioning grave or permanent injury. What we might have expected without that quiet organisation, Russia may show us.

If at any time the decision should be arrived at that in North-Holland, without radical alterations in the hydraulic conditions the general fight against mosquitoes as conducted up to now is not worth the expense, this would not mean (as has been asserted) that we should give it up and sit down with folded hands, but that we should confine ourselves to perfecting the old and tried system of individual malaria fighting (also perfecting it: the introduction of so-called cheaper quinine on the initiative of the former Inspector of North-Holland and Utrecht, Professor Dr. *Aldershoff*, in conjunction with the Amsterdam Quinine Factory is an example of this). This does not in any way exclude the taking of other measures, as may be seen, for instance, from the successful anti-larval measures at Nieuwendam.

Another point of emphasis is the importance af anopheles in houses on the basis of what has been said on page 46. In conjunction with this, the endeavours of the Red and White Cross to induce inhabitants by propaganda to start the fight, must be considered as of the utmost importance.

It is further clear on the basis of what has been said above, that in our malaria areas such an organisation for the distribution of quinine as that of the Italian Red Cross in the Pontine Marshes or of the Commune of Rome in the Agro Romano, would be superfluous. We are really much better of. But if the draining of the Zuyder Zee really reaches the stage that groups of "polderboys" remain there day and night, in an area not yet in the regular possession of our doctors, and later on, during the first few years of bringing the newly won land under cultivation, then a regulation, such as that of the "Istituto autonomo" in the Piave region (page 34) or like that of Chaturka (pages 28 and 43: as regards the latter I chiefly have in mind the parasitological investigation before engaging the men, which is of great importance in an area hitherto uninhabited) might certainly be considered with a view to adoption. Of course I do not mean a slavish imitation, but adoption with utilisation of the many data collected in the course of these years, the great value of which as proof of what can be achieved and what cannot, will perhaps only then, be realised but then certainly.

(*Nederlandsch Tijdschrift voor Geneeskunde*, Haarlem, **69**: 1925, I, Nrs. 2 & 3, p. 139-152 & 218-228)

METHOD OF ADMINISTRATION OF QUININE, PARTICULARLY WITH A VIEW TO MALARIA PROPHYLAXIS ON A LARGE SCALE

DR. J. W. VAN DER SPEK, THE HAGUE, HOLLAND

THE usual methods of administration of quinine are: per os, in solution, cachets, pills, tablets, subcutaneously, intravenously, intramuscularly.

In a brief discussion of the most desirable mode of administering quinine the distinction must be made between the treatment of individual cases and the fighting of malaria on a large scale, for instance, when it is a question of controlling endemic malaria in a particular region.

While, in individual treatment, the doctor will consider which method is the most desirable in the particular case, extensive malaria prophylaxis and control can, by its nature, be effected by means of a general plan only and there must be taken into account an average standard dose, a mode of administration which is accepted without justified aversion and simplicity as regards the keeping and taking of the drug, with a view, among other things, to cost of transport and treatment.

If we consider what are the advantages and disadvantages attending the different modes of administration we may, in the first place, put on record that the common opinion of almost all writers on this subject is that dissolved quinine administered per os provides the most rapid and full quinine effect.

At the same time this method is open to great objections: no success has so far been achieved in correcting the intensely bitter taste of a solution, and consequently many patients, and children in particular, have a violent aversion to this method. It frequently gives rise to obstinate vomiting and it is difficult of application in comatose conditions, in which condition rapid absorption is so essential.

These difficulties are done away with for the most part when quinine is given in pills or cachets or tablets. Pills however must be fresh because they dry rapidly and absorption in the intestinal canal is then

very inadequate. Cachets are fairly expensive; the tablet, provided it is made in such manner that it breaks up in a few seconds, is therefore left as the mode to be selected for administration per os.

As regards intramuscular injection either of quinine alone or quinine combined with urethane, which injections are mostly made deep in the nates, there is some difference of opinion. According to some writers it always produces abscesses and necrosis in the long run. Others again extol this method and apply it readily. On perusing the literature on the subject the impression is nevertheless gained that, in many cases, the abcesses occurring are to be attributed to insufficient asepsis and faulty technique when injecting, and it is not to be wondered at that repeated injections of concentrated quinine solutions at the same point finally result in necrosis; this lies in the nature of the action of quinine on the protoplasm.

But the view that in a particular case a single injection of quinine in the nates is contra-indicated by reason of the danger of necrosis or abscesses appears to me wrong and there are a number of writers who are of the same opinion. I myself have repeatedly given such injections and have never seen any complication.

For some time it used to be pointed out (as for instance by *Borel and Maire* in 1923) that intramuscular injections would cause tetanus or render the latent tetanus infection acute. But this too is now contradicted in other quarters.

Subcutaneous injection finds few advocates. A single drop which gets into the skin on drawing back the needle produces necrosis, and to avoid this, weak solutions, for instance mixed with urethane, have been recommended.

Intravenous treatment is reserved for severe attacks in which it is absolutely indicated, to convey a quantity of quinine direct into the blood circulation. As a regular treatment it by no means yields any better result than any other mode of administration, while it has considerable disadvantages. (Thrombo-phlebitis, cinchonism).

As stated above, the doctor treating a malaria case will have to determine which method he will apply in that particular case.

In the malaria prophylaxis on a large scale however we are confronted with an entirely different proposition.

Needless to say there can be no question here of the application of injection of any kind whatever. Each quinine injection requires strict asepsis and careful technique, the chance of infection appears to be much greater than, for instance, with morphine injections. Therefore if malaria is to be controlled in a lesser or greater region injections are not to be considered.

There remains administration by the mouth.

For the reasons stated above the administration of dissolved quinine is, though not impossible, almost outside the limits of feasibility. The bitter taste and the vomiting are serious difficulties, and unless the solution is prepared on the spot the conveyance of the necessary quantity of solution occasions unnecessary trouble.

Cachets are too dear and therefore pills or tablets are left.

Of these the tablets deserve preference in every respect, they are easy of transport, occupy little space, remain in good condition indefinitely, if properly packed and cost not much more than quinine in powder form. The dosage is the simplest imaginable (this also applies to pills).

Malaria control on a large scale is most easily and cheaply effected by an administration of quinine in tablet form. The therapeutic effect is not inferior to that of other modes of administration capable of application in this case.

MALARIA IN ITALY

THE ANTI-MALARIAL FIGHT: ITS METHODS: ITS RESULTS

(LA MALARIA EN ITALIE: LUTTE ANTIPALUDIQUE: SES PROCÉDÉS: SES RÉSULTATS)

LUCIEN RAYNAUD, ALGIERS

Member of the Health Committee of the League of Nations

". . . . A wild marsh land, with obscure reed huts on the borders of canals, amid cork oaks with reddish trunks, reeds lying motionless on the dead water, the long drawn out and monotonous croaking of frogs and dangerous clouds of gadflys and mosquitoes. Widely scattered around, seemingly shadows, silent shepherds, bending under the yoke of hopeless suffering, as in the ergastulum, women with emaciated faces in which big wild eyes shine, paralysed and deformed children who hang at the breast like orphans without hope. . . ."

Francesco Sapori.

SUCH is the description given a few years ago by an Italian writer of the fatal regions of the Pontine Marshes. This sombre picture was applicable to many other marshy areas of Italy. To-day matters have changed. True it is that the entire malarial surface of the Peninsula has not yet been improved, but persistent work and efforts have profoundly modified the situation.

This was the fact recorded by the Commission which had been instructed by the Health Committee of the League of Nations to study malaria in Eastern Europe and Italy. We give here a summary of the conclusions of the report concerning Italy presented to the September (1924) session of the Health Committee of Geneva.

The extent and importance of malarial fever in Italy constitute it a social problem of the first rank. The question is dominated by two factors: in the first place we have the orography and the climate which have created suitable conditions for the appearance and persistence of the infection, and on the other hand, the necessity of getting rid of the marshes, the cause of the illness, transforming them, "bonifying" them, so that they might furnish sustenance to a numerous population.

To this task the Government, engineers, agriculturists and doctors have devoted themselves; and it is impossible to over estimate the progress achieved in the struggle against this infection by the scientists of the country who studied malaria.

A belt of high mountains surrounding, almost in a complete circle, the immense plains of the North, a mountainous skeleton, less elevated, but of great length traversing the whole of the rest of the Peninsula and occupying more than half of its surface, such is the geographical formation of Italy. An exceedingly abundant river system, more than 300 rivers and torrents descending from these heights, on the other hand, have, in the low parts, created a very fertile alluvial soil, which towards the seashores, form heavy deposits of fertilising material and resulted, owing to volcanic movements, erosions, accumulations of dunes, in forming an obstacle to the normal outflow of the waters; marshes and ponds without number were formed pretty well everywhere and particularly near the estuaries. The hot climate and stagnant water are the most favourable conditions for the multiplication of mosquitoes; Italy was marked out as a prey to malaria.

She has been so in all times. Some parts of her soil nevertheless admitted of being worked, improved, reclaimed; the historical political events of which Italy has so often been the scene in former times, caused the work to be abandoned; plains formerly fertile were deserted and became marshes; men fled to the hills.

The rapid increase of the population in the last century (it has almost doubled in fifty years) concurrently with the reconquest of unity and safety, led to space being sought for on which new generations might settle and find their sustenance. It was proposed to drain the marshes with the idea that malarial infection would be got rid of at the same time. The hygienic result was good in certain regions, less so or slower in others, but from the agricultural point of view the effect was such that the State thought itself in duty bound, following the example set by the "Magistrato alle Acque" of the ancient Republic of Venice, to give greater extension to the works of *great bonification* or "redemption" of marshlands. The laws of 1878, 1882, 1883 laid down the conditions under which this work was to be carried out; but it was perceived that there was no agreement between hydraulic improvements and the improvements of farmers, and above all that malaria far from being extinguished, often extended along the artificially created drainage channels.

Discoveries regarding the parasite and the transmitting insects, modified both the means of combating the disease and the methods employed by the owning or reclaiming land-owners or associations.

The law of 1900 created the *Institution of State quinine* as a curative and preventive remedy placed within reach of all. The laws of 1901, 1902, 1904 and 1907 completed this organisation. Malaria was considered as a *professional disease* for compulsory declaration;

the land-owner was compelled to look after and safeguard his workmen, to indemnify the family in case of death if it had occurred owing to lack of precautions or aid in the *zone officially declared infected.* Finally, all the profits of the sale of the quinine prepared by the State were to be reserved for the more energetic continuance of the struggle.

The State being unable, in spite of its large sanitary staff and its very complete equipment, to undertake alone the defence of the territory against malaria, called in the aid of charitable associations, such as the *Red-Cross*, the *Autonomous Institute of Venetia*, the *National Institute for the Pontine Marshes*, the *National Association for the South*, *etc.* It granted them very high subsidies and placed scientists, bacteriologists and inspectors at their disposal.

Thus there were created in the whole of the infected regions, 1200 permanent or temporary out-patient departments in addition to 2,000 out-patient departments (consultation surgeries) of a general character normally existing, *quinine distributing stations, ambulances, sanitary stations, anti-malaria sanatoria, mountain and sea colonies*, school medical services, in which the children, while receiving education, *are daily treated with quinine, anti-malaria schools* where the methods of combating are communicated to doctors, nurses, teachers, etc., laboratories for the examination of the blood, laboratories for research in connection with mosquitoes, commissions for the study of small bonification (small measures for the destruction of larvae, etc.).

One of the last important legislative enactments is the decree of the 31st December 1923, modifying the Italian sanitary organisation and co-ordinating all measures and all works effected by the various Ministries, in order that the Direction of Hygiene may exercise its right of supervision thereover; this means a linking up and hygienic co-operation in the work of reclamation.

It is no longer possible for marsh drainage to be carried out without the subsequent measures required for the disappearance of the small ponds and the outflow of small streams and removal of grass being provided for. The associations and owners of improved lands must avoid any cause which may aggravate the sanitary situation by reason of the bad drainage of the surface waters.

What has been the result of these works as a whole? *In 1885 only two Provinces of Italy were free from malaria; in 1887 there were 21,033 deaths* due to that illness. The illness spontaneously fell off until 1900, under the influence no doubt of the general conditions of hygiene, which at the same time resulted in lowering the general rate of mortality and the death rate from contagious diseases. In 1900,

a sudden rise! There is an advance from 10,811 to 15,865, followed by a regular descent. The law of 1900 on quinine hardly seems to have produced any change before 1904, when the mortality is 8,465, but the downward curve becomes more marked from year to year, reaching the figure of 2,045 in 1914.

The war, for many reasons, resulted in an increase which, in the influenza year, produced 11,487 deaths, but in 1923 the curve had almost resumed the pre-war level with 2,274 deaths.

Italy forty years ago formed one immense focus of malaria; at present the officially infected zones only occupy about one-third of the total superficies. They comprise a part of the Lombardian Plain, Emilia, and the coast of Venetia, as far as Istria; this northern region is the one where the cases are mildest; on the contrary, the Mediterranean coast and the south of Italy, the Adriatic plains of the Abruzzi and the Molise and Apulia, then the coasts of Calabria, as well as the whole of Sicily, and above all, Sardinia, are stricken with malaria in a grave form.

At what cost has this result been achieved?

The profits on the sale of quinine from 1908 to 1923 were, in round figures, *24 million lire*, of which more then *17 million have so far been devoted to the struggle* in the form of direct expenses or subsidies to the associations participating in the defence work. To this there must be added the expenses of the provinces and the colonies (Rome has a malaria budget of 1 million per year), the associations and land-owners.

In addition there must be put down on the debit side the sums appropriated by the Ministry of Public Works for works of *great bonifications* which in sixty years, represent more than *half a milliard.*

It may be said that during the last twenty years, the State has expended for the reclamation of marshy soils, particularly in the provinces of Venice and Rome and for human bonification, that is, anti-malaria defence in man, a sum which annually may be estimated at 17½ million lire.

Conclusions.

It seems that we may sum as follows the results of our observations and our data as to the causes and conditions of malaria in Italy, as well as the methods used or advised by the sanitary administration and malaria specialists in the struggle against this grave infection:

1. Italy found itself under the most favourable geographical and climatic conditions for the occurence of malaria;

2. It was a matter of necessity to Italy, in view of the small extent of its surface suitable for agriculture, and the growth of its population, to look for lands for intensive cultivation at the expense of its marshes;

3. The anti-malaria legislation taking its inspiration from scientific discoveries, introduced hygiene into the great work of reclamation of marshy soils; but it is above all the *law on State quinine*, which, by allowing of a liberal distribution of this product for treatment and prophylaxis, resulted in an indisputable reduction of the reservoir of virus;

4. The immense effort of the Government and the charitable associations has reduced to one-third the declared malaria area of the peninsula and has in particular resulted in a noteworthy decrease in mortality and morbidity;

5. Of all the means used in Italy the greatest importance is attached to great bonification with its hydraulic, agricultural and hygienic conditions; but in order to be effective it must be accompanied for a long time by an aggregate of carefully supervised measures;

6. *Human bonification*, that is, the definitive cure of the patient and temporary quinine prophylaxis of the exposed individuals certainly constitutes what all Italian malaria specialists consider as the essential point of the struggle:

7. *Mechanical protection* and the *destruction* of winged insects are among the small measures most reccommended by the same scientists;

8. *Anti-larval measures* are useful, above all in the immediate environs of inhabited places; their application is a question of circumstance and place;

9. Finally, *biological protection* by farm animals appears in certain localities to give such results as to justify further investigation;

10. *The reclamation of a country and its return to health cannot be done in a day.* It is the results of lengthy agricultural work (including large scale reclamation), of the constant modification of the soil so as to utilise all the surface water, the prosperity of land-owners and their labourers, the more comfortable installation of their dwellings, their better hygiene, in short, of the wellbeing they secure and also of their general education, all of them conditions which place them in an excellent posture of defence.

It may be said that, in the last resort, it is the well-being of the population which results in the transformation and disappearance of malaria.

(*Presse Médicale*, Paris, 19 nov. 1924, No. 93, p. 1951—1953)

HYGIENE IN ALLIANCE WITH NATIONAL AND UNIVERSAL ECONOMY

(DIE HYGIENE IM BUNDE MIT DER VOLKS- & WELTWIRTSCHAFT)

PROF. DR. REINER MÜLLER, COLOGNE

Ordinary Professor of Hygiene and Bacteriology

IN universal economy, malaria has, up to this day, presented the principal obstacle to the conquest of the tropics by European civilisation. It was frequent with us as late as 90 years ago in Aix-la-Chapelle, Jülich, Grevenbroich, Duisburg ; it now appears in Russia again as a concomitant of the disturbed order of affairs, up into the far North, including even Archangel. In India, out of 325 million inhabitants at least 100 million fall sick with it every year, several million of them dying. Thus in 1917, in India, more than 4½ million deaths from fever were reported, in which malaria played a chief part. The people who are under the scourge of this illness may be assumed at 800 million. But we are no longer powerless against it. We know the cause, the protozoon which destroys the blood corpuscle, we have for 25 years known the carrying vehicle, the Anopheles fever mosquito; moreover we now have a really good remedy for the disease. Already the tropics have lost much of their terror. They are no longer the grave of the European, as Batavia was once called.

It almost seems as though now the United States in particular desire to utilise the bases created by science for a social fighting organisation on a great scale against malaria. There, in the sub-tropical Southern States, there are still wide stretches of territory, bigger than Germany, in which agriculture and economic conditions are very backward. In the Mississippi settlements, malaria, this marsh fever, frightens the settlers away in spite of the enormous stretches of exceedingly fertile soil.

The health pioneers of the Rockefeller Foundation six years ago undertook to show in several places, that malaria can be eradicated, even in the very midst of plague-stricken environs, as in the district

town of Hamburg in te State of Arkansas. In 1916 there were there, among only 1200 inhabitants, 2205 cases of malaria reported. The year 1917, during the first 4 months, again showed as many cases as 1916. In April 1917 the fight started and during the last 9 months of that year there were only 122 cases as against 2073 in the same months of 1916. In 1918 there were only 59 malaria cases, in 1919 only 35, in 1920 129; 1921, only 11 among 1600 inhabitants. And this in spite of the fact that in the environs the fever continued to rage in the same old way. And what was the cost of this restoration of the transatlantic Hamburghers? In the first year 1917, 1 dollar 45 cents per head of the population, and in the following years only 42 cents, 69 cents, 81 cents, 63 cents. Taking an average of 35 towns it was found that if the struggle had once been going in a town at a cost of slightly more than 1 dollar per head for one year, only 25 cents more per head were required to make the results permanent and keep the towns practically free from malaria.

The economic justification of this fight is clearly evident. The expenses alone per annum per head of the population, for malaria formerly exceeded 2 dollars, apart from all the unpleasantness, and danger of sickness. And that is precisely what the Rockefeller Commission wanted to show in these regions, that to keep healthy is much cheaper than being ill and that it is possible to remain healthy, even in those hot regions.

(From the Commemmoration speech on the third foundation ceremony of the University of Cologne, 1923, p. 12—13).

ON WAR MALARIA

(UEBER KRIEGSMALARIA)

LECTURE OF THE DIVISION FOR TROPICAL MEDICINE OF THE GERMAN COLONIAL CONGRESS ON THE 17th AND 18th SEPTEMBER, 1924

PROF. H. ZIEMANN, BERLIN

DURING the world war the extension of the scene of operations created the conditions for dissemination of malaria, both in the army and in the civil population. Thus it was that in the German Army, cases of malaria reached the highest figures, apart from sexual diseases; there were recorded in the first year of war 0·35‰, in the second year 1·32‰, in the third year 6·2‰ and in the fourth year 13·7‰. The speaker shows by means of curves that the maximum number of increases occurred between July and October, but that the annual curves show a second apex in April to June.

In *foreign armies* the morbidity and mortality from malaria was much greater than in the German. On the English Salonika front, according to *Phear*, the cases in 1916 and 1917 were about 333‰, in all three years together 1053‰. The malaria mortality was in 1916:2·02‰, 1917:1·17‰ and 1918:1·69‰; according to *Wenyon* it was nearly 9 times less than among the French.

Owing to the return of *germ carriers* malaria again spread strongly among the *home civilians*; according to the communication of the Federal Health Office there were reported among the civil population, 1918: 4311 cases; 1919: 3157 and 1920: 877 cases. By far the worst was the Government Division of Aurich, with 4009 cases in 1918. Individual cases were even observed in large towns. Since 1919 cases of perniciosa also occurred in Germany, there were more than 70 known, of which only 17 had been in the field, while 13 had never left Germany. From England and France likewise the occurrence of autochthonous cases was reported.

According to *Külz*, *Bagdad*, formerly free from malaria, was infected by the influx of germ carriers, and according to *Ziemann*, this was also true of the *Lebanon Mountains*, formerly almost entirely free; later reports state that the latter are again almost entirely free.

The widest dissemination of malaria however occurred as a result of the civil war and famine in *Russia*, where, according to *Mühlens*, it extended as far as Archangel.

The speaker then deals in detail with possible *sequelae* of malaria in so far as they are likely to affect the question of injury due to military service: pernicious anaemia, leucaemia, polyglobulia, cachexy, skin diseases; in splenic tumour he is of opinion that a permanent chronic tumour of the spleen should not occur after energetic treatment; rupture of the spleen did not occur during the war, swelling of the liver, lung symptoms, heart symptoms, kidney affections, diseases affecting the nervous system, which latter in particular played a great part under war conditions.

From the *therapeutic* standpoint, in war malaria, the cinchona alkaloid still stands at the head. The speaker says that the view he has advocated for years, that quinine does not act directly but indirectly on the parasites, has been confirmed by later investigations by *Mühlens* and *Kirschbaum*. He recommends treatment by minimum daily doses of 1·2 gram, in perniciosa twice 1·0 or four times 0·5 up to 8 days after decline in temperature, then 2 days pause, 2 days quinine, 2 days pause, 2 days quinine, then 6 to 8 weeks 1 gram each Wednesday and Saturday. His quinine prophylaxis consists of daily doses of 1·2 gram every Wednesday and Saturday (twice 0·3 gram morning and evening).

In foreign armies larger quinine doses were given in part, thus the *Italians* had a daily *quinine prophylaxis* of 0·4 gram and in badly infested regions 0·8 gram daily.

The question of *quinine resistence* is of great importance. The speaker distinguishes three kinds: 1. occasioned by the parasites taking up their preferential abode in internal capillary regions; 2. that due to endogenous quinine resistence of certain races of parasites; 3. that consequent upon absence of powers of immunity in the patient. The latter form no doubt occurred most frequently in war malaria. Therapeutically the resistent war malaria was still found to be most favourably influenced by the combination of powerful quinine plus neosalvarsan treatment.

Finally, the speaker sums up his war experiences to the effect that malaria, in spite of the heavy sacrifices it entailed both during the last world war and since, can be combated with considerable success, given energy and the use of the right means.

During the *discussion A. Plehn* says: The clinical peculiarities of war malaria culminated in the obstinacy with which it often resists quinine treatment. The *action of quinine* no doubt consists of a *stimulus*

which indirectly releases or increases the counter-action of the organism itself. According to the biological law of *Arndt-Schultze* small stimuli, assist, large ones inhibit, very large ones paralyse. Very large doses of quinine would therefore, to say the least, yield no advantage. A condition precedent in each case is a certain capacity for reaction of the organism, which is undoubtedly in part conditioned by psychic factors. If this is lacking then the largest quinine doses are ineffective or are even unfavourable in their action. Under this heading come the greater part of the refractory cases of war malaria.

Claus Schilling: According to observations on service men, malaria dies out after about 3 years. Malaria in Germany has rather fallen off than increased since the war. By the instructions of *Otto*-Berlin, *Schilling* also states: as early as 1906 *Krulle* pointed out that by the carrying out of quinine prophylaxis in the German Expeditionary Force in China the occurrence of new cases was shifted to the following year. A like observation was made by *Otto* at the Narocz Lake; two divisions which were in that region in the previous year had, in the spring of 1917 more cases than one which had newly arrived, while on the other hand, in a division transported to the West, in a region free from malaria, in the spring of 1917 more cases of malaria occurred than in 1916 in the East.

Fülleborn: Without quinine prophylaxis during the world war, in heavily infected malaria regions, practically *all German* men on service would have been unfit for service after as little as 2 or 3 weeks owing to malaria, so that it would have been necessary, though utterly impossible, *entirely to replace repeatedly the men in each malaria season.* What we should have had to expect from the Wardar troops, without quinine prophylaxis judging according to the anticipated course of the annual epidemic, is absolutely monstrous. Quinine prophylaxis was an absolute military necessity and in formations where it was *not only prescribed, but carried out under strong control,* not only among us but also in the Entente troops, it was found thoroughly effective. It is true that there is no form of quinine prophylaxis which can with certainty prevent malaria, neither the periodic with large quinine doses nor the daily with smaller doses, which presents many advantages in military practice.

As regards the *origination of quinine proof races of malaria parasites* the theory of selection suggests itself; against this however there is the fact that in Italy where quinine prophylaxy has for decades been applied among the population on the most extensive scale, nothing is heard of such malaria races which have become proof against quinine. Though the occurence of such a race of parasites is

not disputed, the reason for the frequent failure of quinine in the war, — both in therapeutic and prophylactic treatment — was often the *bad condition of nutrition* of the men. Undoubtedly however many of the apparent "quinine-proof" malaria cases *failed to take the quinine* prescribed *at all*, particularly as foolish reports had got about as to the injury occasioned by quinine (for instance, impotence resulting).

(Report by Prof. *E. Steudel*, Berlin-Dahlem in *Archiv für Schiffs- & Tropen-Hygiene*, Leipzig, **28:** N. 11, 1924, p. 502-509 Summarized)

ON THE INTANGIBILITY OF THE DOGMA OF PREVENTIVE QUININE AND ON THE CAMOUFLAGE OF MALARIA BY THIS MEASURE OF PROPHYLAXIS

(DE L'INTANGIBILITÉ DU DOGME DE LA QUININE PRÉVENTIVE ET DU CAMOUFLAGE DU PALUDISME PAR CETTE MESURE DE PROPHYLAXIE)

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SINCE the time when Count de Bourneval, in 1717, at the siege of Belgrade, preserved his men against malarial infection by distributing quinquina to them, the question of quinine administration for preventive purposes has been constantly under discussion. Advocated by some, decried by others, it has been nevertheless applied with fair regularity in the course of remote expeditions and in our possessions overseas, but with some diversity of result, so that a definitive formula accepted by all hygienists has not yet been established. Nevertheless, as we will endeavour to prove by a number of observations made in the wards of the Hospital of Saint-Jean at Beyrouth, the question might be solved to the satisfaction of everybody, provided there is clear understanding as to the object in view and the necessary doses to attain it. If pernicious attacks are to be prevented and malarial mortality reduced, the necessary quinine prophylaxis will work wonders. If malarial infection is to be avoided, quinine, in the doses which the organism will stand without injury, cannot do otherwise than reduce the number of sufferers and render the course of the illness more favourable, but it will also create the danger of masking the first attacks, thus putting the clinical sense of the medical man to a severe test.

In the course of the last Syrian summer, the one just ended, which extends from June to the end of October, 81 malaria sufferers entered our department. Among this number there were 43 cases of first malaria attacks observed in soldiers coming from France, who had not previously lived in an infested region. Of these, 17 had on their

hospital order the words "malaria" or "probable malaria"; 38 others arrived under various headings and their malaria would have escaped attention were it not that every case of fever not explained by a sufficient organic lesion or not consonant with the other symptoms observed, was systematically submitted to checking by blood test. With these patients it would indeed have been difficult to ascertain clinically the existence of malaria, as the symptoms observed and the thermic curve did not in any way point to the right diagnosis. The temperature was often not very high, speen enlargement was absent or late; the attack when it occurred was in rudimentary form, or else its different phases did not exhibit the characteristic features which are generally so clear and well defined, it being only possible to identify one of the pathognomonic elements of which it is usually made up, and in most cases heat, shivering and sweating being inferred rather than observed; the heat was limited to a few fits or simple congestion of the face, shivering was reduced to greater sensitiveness to cold, sweating was not very pronounced, only remotely resembling those profuse perspirations which bathe the patient and flood the bed. With these features the attack, thus masked by the toning down effects of quinine, just as it did the announcement of slight gastric disorder, and above all it suggested the outbreak of that famous three days fever which is very common in Syria, and the diagnosis of which is unfortunately, every day, with regrettable thoughtlessness, made, instead of malaria, which latter would be brought out clearly by a trial treatment, failing positive hematological examination, even in those numerous cases in which preventive quinine has expelled the hematozoon from the peripheral circulation. The poorly defined symptoms just enumerated are not such as to point to a special form of hematozoon. Those of our patients, the lesser number it is true, who, owing to indolence of the persons in command of units, or owing to lack of personal conviction, had evaded the preventive quinine treatment which is compulsory in the East, had presented a first typical invasion with perfectly classical attacks of fever. But others again, classed as perfectly reliable and wellminded men, of whom we asked the truth with the object of scientific enquiry, and who had regularly taken every day 50 to 80 centigrams of quinine hydrochloride, had nevertheless contracted malaria and exhibited a perfectly typical evolution. Quinine, as many observers have pointed out before us, therefore, does not always prevent malaria, and for that reason many practitioners who have not been put on their guard, allow themselves to be misled owing to the masking of malaria infection by the preventive quinine. This masking is, in itself, a proof of

the hindrance which quinine places in the way of the growth of the hematozoon in the blood and is an encouragement towards maintaining the method. Furthermore, although our cases were sometime particularly grave, with prolonged hemolytic icterus and profound anaemia, which compelled us to send 17 patients home to France, we did not record a single pernicious attack and have had not a single death to deplore, a fact which still further defines the prophylactic administration of the salts derived from quinquina, from the mere point of view of humanity, in spite of the enormous cost of the drug at the present time. This drug properly administered therefore, almost certainly prevents death and often alters the course of the disease for the better; that is sufficient reason why it should be persistently used in ample doses to the great benefit of our soldiers and the maintenance of our strength in outlying spheres of operation. By a sort of irony, the only difficulty which preventive quinine administration creates is for those who have the duty of applying it. Quinine salts, as we have already stated, influence malaria manifestations to such an extent that diagnosis is thereby rendered faulty. Let medical men therefore be advised of these facts, let them constantly maintain watchfulness and not hesitate to have recourse freely to the laboratory which, in very many cases, will alone enable them to strip the mask off malaria, which presents itself to them under such deceptive aspects.

But, the reader will say, surely it is not possible to make a blood test for all patients admitted into the hospital establishments of an army. There are moreover many garrisons where it would not be possible to carry out such tests habitually. We will only say in reply that prophylaxy is a chapter of hygiene during the campaign and that the military doctor, who is always at the same time a hygienist, may be led to suspect the existence of malaria by a well conducted enquiry. The conditions which lead to the occurrence of malaria may be summed up in a very simple equation: reservoir of virus + anopheles = malaria. In the region traversed or occupied are there or have there been malaria sufferers? It is certain that this region is favourable to the development of the anopheles and if ponds and stagnant waters still exist there, although malaria may seem to have disappeared, its reappearance must be feared with the known arrival of new reservoirs of virus. At that moment a drop of blood taken and spread on a slide and forwarded to the nearest laboratory, if it shows a positive result in a single patient having come from France and not having left the region, is sufficient to establish the certainty that malaria is about to develop in endemic or epidemic form and then that the

systematic search for malaria must be persued methodically in the hospital wards, bearing in mind the anomalies created by preventive quinine.

On our arrival in Beyrouth in the month of May last it was a matter of public notoriety that there was no malaria in the town. In the course of previous years the doctors who had preceded us had only observed a very limited number of malaria infections. We ourselves, in the course of the last summer, were able to observe only a single case which had been actually contracted in the town. But the perusal of the inevitable Bædeker had taught us that the region of the river of Beyrouth to the east of the town was an unhealthy region and that a little further on, a stream, the Nahr-El-Mot (River of Death) owed this appellation to the unhealthiness of its banks. Through conversations with the local doctors, most of them former officers of health in the Turkish Army during the Great War, finally, we knew that the Turkish, German and English troops which had successively occupied the town had taken care not to camp in this river region, and had given preference to the red sands of Saint-Elie to the south. These facts led one to apprehend a recrudescence of malaria in a region where forms of the anopheles were habituated and where they would, without fail, resume their nefarious action upon the favourable arrival of the reservoirs of virus contributed by the host of emigrants, Armenians and Greeks, fleeing from Turkish reprisals, who were installed there in indescribable hutments, amid sordid filth, and surrounded by stagnant waters. Failing this it might also have been feared that our Colonial natives, Annamites, Malgaches and Senegalese frequenting the shops of the army base in the vicinity of the railway station near the river might, in themselves, constitute small reservoirs of virus and allow of the revival of malaria, because during the war malaria was seen to appear in France in regions which had till then been free, on the arrival of Colonial sharpshooters. A first case of malaria observed in a soldier coming from the home country and who had never left the region of the river, opened our eyes and made us alive to the necessity of hematological test of all patients coming from the naval base of the army and its vicinity, naval wireless operators, military nurses, clerks and workmen of the administration, soldiers of the army aviation park, all of them having bivouacked and being grouped in hutments in the suspected region. Thus, in spite of the preventive quinine, there were discovered these 17 patients which the clinic alone was able to identify, and the more imposing group of 38 soldiers with disguised malaria, an impressive total which to-day rightly gives great concern to

the supreme command of the army and the civil hygiene services of of the greater Lebanon.[1]

Subject therefore to the knowledge by practitioners, of the difficulties placed in the way of the tracking out of malaria by the prophylactic administration of quinine salts, the principle of the preventive use of quinine remains unshaken. Could it not however be at least extended to the doses to be given? It is well known that the disappearance of the blood parasite in the organism can only be obtained sometimes with 1 to 2 grams of quinine per day, by repeated series of treatments. In order to take the right course and be absolutely sure of preventing malaria, these same quantities of medicine must be given regularly during the whole time the danger of malaria lasts. It will readily be understood that so active a course of chemical prophylaxy, which is dangerous to the gastric mucosa and to the delicate nervous terminations of the labyrinth of the ear, would only be possible in the course of military operations of short duration in a particularly infested zone. We, for our part, should not hesitate in practising this heroic prophylaxy in a particularly unhealthy country in the course of a military operation not exceeding one to two months. But in the colonies and in particular in Syria, where quinine must be given all the summer, that is, from the beginning of June to the end of November, only a more modest object can be pursued, that of preventing the pernicious attack, modifying the evolution of malaria and diminishing, if possible, the number of persons affected thereby. Since the beginning of the XVIIIth century all observers who have fought against malaria have aimed at no other result, and we can do no better than model our course on that pursued by them before us. A rapid review of the means used and the success recorded by these forerunners would then, of necessity, lead us to-day to a doctrine applicable to all.

In brief, in the course of the last two centuries, the prophylaxy of malaria has been applied on three methods all of which number successes. Some practitioners, such as *Collis* in Malacca, *Bizardel* in Senegal, *Sezary and Cornebois* in Algeria, *Quennec* at Majunga, *Saint-Macary* in Dahomey, *Bianchi* in Italy, *Salanoue* in the Soudan, had recourse to weak daily doses of 10 to 20 centigrams. Some, such as American doctors during the war of Secession, *Lanel* at Ouargla,

1. This study was closed on the date of the 31st October 1923; other malaria sufferers coming from the region of the river are still arriving in our ward, as the summer this year encroaches on the month of November. Further patients have also been identified in other wards, and in the course of health inspections on the spot.

Vincent and Burot, Caylay and Plehn in the Cameroons, preferred medium doses of 30 to 50 centigrams *per day*.

Others, finally, as *Thorel* on the banks of the river Mekong, *Groesser* at Priok, *Michon* in Corsica, *Kuelz* at Kleinpopo, *Ziemann* in the Cameroons, adopted the intermittent administration of strong doses varying from 60 to 80 centigrams once a week (*Thorel*) to 1 gram every four days (*Ziemann*).

As is clear from this, the prophylaxis of malaria appears — though it is more appearance than reality — not to correspond to unity of views. The fact is however that though practitioners are almost wholly won over to the invioliability of the doctrine of preventive treatment by quinine and the reality of the results to be expected from it, they were unable to apply a uniform method in all the regions where they practised it. They had to take into account the intensity of the malarial infection and the gravity of the clinical forms encountered. Thus, *G. Alvaro* records that the small daily doses in the Italian Army gave him better results than massive weekly doses. *Robert Koch*, on his part, thinks that 50 centigrams every three days will effectively combat the growth of the blood parasite and "that a larger dose would be badly endured and should not be employed except in cases where infection is to be feared". Finally, *Laveran*, considering that quinine would form an obstacle, not only to infection in persons free from malaria, but also arrest an initial infection and prevent relapses in already infected subjects, gives preference to medium intermittent doses. Thus a single line of conduct in all cases and in all countries cannot be adopted. Does this mean however that the prophylaxis of malaria cannot be translated into a small number of formulae? We think this is perfectly possible. If the region of operations is but slightly infested, if benign tertian and quartan are observed, which are but infrequently the generators of pernicious attacks, and if the stay in the country is to last for many months, a choice may be made between the method of small daily doses (*Alvaro*) and the intermittent medium dose method (*Koch and Laveran*).

If the country occupied is badly infested and malignant tertian and pernicious attacks are observed, if it is to be traversed in a few days, recourse may be had to heavy daily doses of 75 centigrams (*Vincent and Burot*) and even up to 1 gram, as we should advocate. If the duration of stay exceeds 1 month, *Laveran's* method of the intermittent medium dose must be applied.

If we desire to apply the foregoing data to Syria and the Lebanon in the light of the observations made in our hospital wards, which inform us on the origin of the cases by means of interrogation, and on

their gravity by the clinical evolution, we should willingly, as in the Navy, and after the manner of *Alvaro*, give 50 centigrams of quinine hydrochloride daily to the troops quartered in the region of the river where no doubt the malignant tertian rages, but where preventive quinine has hitherto warded off pernicious attacks; we should on the other hand give 80 centigrams every two or three days, after the manner of *Michon* and *Laveran*, to the troops of Alexandria, El-Hamman and Rayack, from where the most serious cases reached us with pronounced hemolytic icterus and marked splenomegalic anaemia . . . And we may now sum up this study as follows:

1. The dogma of preventive quinine remains intangible.
2. Its application must be guided by the intensity of the infestation, the duration of exposure to contagion, the clinical forms observed, the character of the parasite identified.
3. This application must choose between three methods: small daily doses, intermittent medium doses, heavy daily doses, exceptional, applicable to military operations of very short duration in a very dangerous region.
4. Quinine hydrochloride is the salt which must be preferred owing to its greater solubility and its lower attacking powers on the organism.
5. Preventive quinine must not be expected to bring about the disappearance of malaria, which it is not always able to do, but there is the certainty that it will reduce the number of persons affected, will favourably modify its clinical evolution and will, with certainty, ward off the pernicious attack.
6. But doctors will, once for all, be put on their guard against the possible masking of a malarial attack by the chemical prophylactic treatment.

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SOME LINES OF CONDUCT IN MALARIA THERAPY

(EINIGE RICHTLINIEN ZUR MALARIATHERAPIE)

PROF. HANS ZIEMANN, BERLIN

From the Pathological Museum of the University of Berlin

IN compliance with the invitation of the publisher, there are set out below in exceedingly brief form, the most important points of view *for the practitioner* which, in my opinion, apply in modern malaria therapy.

As regards details and justification, reference may be made to my monograph, the third edition of which was published in September last (1924), on malaria and blackwater fever (Leipzig, J. A. Barth).

The nature of malaria may of course be assumed to be known to the reader. Nevertheless the fact may be specially recalled that in many cases, for instance in parasite carriers, all traces of fever may be absent, and again, in active malaria, during the feverish attack, the shivering stage may fail to appear (especially in the pernicious form, *R. Koch's* tropical form), further in new sufferers from malaria perniciosa splenic enlargement may be absent, and above all, in the pernicious form again, malaria parasites may be absent from the peripheral blood *at the beginning of the attack.*

As is known, the latter sporulate preferably in the capillary regions of internal organs, so that sometimes a positive result in the peripheral blood can only be found several hours later.

It should therefore always be made the rule to repeat the blood examination a few hours after a negative result, when malaria is suspected, the more so as, especially in regions infected with perniciosa, the latter may appear in the most varied clinical forms of any other protozoon or bacterial infectious disease, and consequently, without blood test, is still often not recognised (frequently mixed infections with the above mentioned diseases also occur). The extreme importance of the blood test is perfectly evident from this. Anyone not able himself to diagnose the parasite should at least send a *"thick drop preparation"* and a thin uniform blood film, each on a preparation slide, to the nearest blood testing office. (The Haemato-

logical Institutes also send out corresponding instructions). For the thick drop preparations it is sufficient to dab out a drop of blood of the size of a large lentil to the size of a halfpenny, allow it to dry completely in the air, then to dip it twice in cooled boiled water, put it on its edge to drain and forward it, after complete drying.

General rules of quinine treatment.

If the diagnosis is determined with certainty microscopically (or with sufficient reliability clinically) energetic therapy must start at once. The more energetic and rapid the latter the greater the prospect of thorough cure and prevention of the formation of sexual forms and consequent dissemination of the malaria.

Quinine is and remains the specific against malaria however much latterly attempts may have been made to decry its value. The view I have advocated for years, that quinine acts on the parasites not directly, but indirectly, has been still further strengthened by recent in vestigations of *Mühlens* and *Kirschbaum*.

As quinine acts with most certainty on the *young*, asexual forms and but little, or sometimes not at all, on the sexual forms, it is important that quinine be applied chiefly when in sporulation the divisional forms separate, i.e. some (2 to 3) hours before the fever attack expected.

The *quinine preparations* for *general practice* are, above all, *quinine hydrochloride, sulphate, quinidine* or recently a mixture of all quinine alkaloids (in East India the so-called Cinchona febrifuge, in Germany, Neopanchinal (*Dr. Schmitz*, Breslau); the average daily dose for each preparation is 1 to 2 grams. According to the statement of Messrs. Zimmer & Co., 1 kg. of quin. sulph. costs 87 Mks., quin. hydrochlor. 100 Mks., quinidine 70 Mks., but the very effective hydroquinine 220 Mks.

Quinine sulphate or quinidine should be taken far more extensively than hitherto, because the therapeutic effect is almost equal to that of quinine hydrochloride, while that of quinidine is even undoubtedly superior in cases which resist quinine.

I do not recommend administration in liquid form, as most persons acquire increasing aversion to the bitter drug, in spite of the addition of correctives. It is best to take it in the form ot tablets, readily soluble in water or in gelatine capsules or cachets. *I found it very pleasant, particularly for children and other difficult persons, to administer it in one tablespoonful of marmelade, which entirely surrounds the bitter medicine and dispenses with the expensive quinine chocolate tablets, or the still more expensive and less bitter substitutes,*

(*Aristochin, Euchinin*). Psychological factors then appear to render absorption more rapid and complete in children.

Preferably the quinine should be given about 1 or 2 hours after a meal, as then the increased secretion of gastric juice allows of speedier absorption of the quinine. On the basis of more recent investigations it does not appear necessary any longer to administer quinine as formerly, with diluted HCl.

In vomiting and all derangements of intestinal activity and above all in all new cases of perniciosa, quinine should be given in therapeutic doses, *intramuscularly*, to ensure absorption, in the form of quinine urethane 0·5 to 1 gram, in the upper external part of the gluteus maximus. The contents of the ampullae must however, after being drawn up into a large Record syringe, be diluted with at least 5 times the volume of sterile solution of 0·85% NaCl. If the contents of the ampullae, as is unfortunately done in almost all cases, are injected undiluted, painful quinine deposits will unquestionably form after several injections. Ample massage is desirable.

In cases of danger to life, particularly with comatose malaria, quinine urethane 0·5 to 1 gram of 0·85% NaCl solution should be administered *intravenously*, but the injection must be made *very slowly* in order to avoid collapse and never more than 0·5 gram at a time. *Children*, in whom the malaria often takes a very typical course (without a typical shivering attack) should be given 0·01 gram of quinine for each 1 lb. of weight.

Special.

In ordinary non-resistant tertian and quartan, the rule is generally to be adhered to as far as possible that quinine is given in doses of 1 gram 2 to 3 hours before the attack is expected, because the quinine level of the blood is then at its highest at the moment of the attack, after this daily at the same time 1 gram of quinine until defervescence or disappearance of the asexual forms.

In ambulatory and mass treatment and above all in new cases, I urgently recommend giving 1 gram *immediately* after diagnosis, no matter in what state of development the parasites are, and so on daily, until their disappearance. There is *no* stage of the asexual parasites which remains *uninfluenced* by quinine. Persons of strong constitution may even, without hesitation, be given a second gram of quinine at the end of the attack.

2. *In perniciosa, during the days of fever as a rule 2 grams of quinine daily either twice 1 gram or 4 times 0·5 until defervescence* or disappearance of the asexual forms. In new cases I, in principle, administer,

during the *first 3 or 4 days*, either 1 gram of the above quantity in one operation, or in two injections of 0·5 each day. In *recurrent* pernicious malaria, in which profound and regular intermissions occur, the total daily quantity of the quinine should, if possible, be given during the intermission, that is, at a time in which pigmented signet ring parasites are visible in the peripheral blood, as then the young forms resulting from division can be got at.

It is a fact that among all nations, during the world war, perniciosa was often combated with far too little energy.

After-treatment.

a. In ordinary tertian and quartan. After disappearance of the asexual forms or defervescence for a further 8 days 1 gram of quinine per day, then 2 days pause, 2 days quinine, 1 gram, 2 days pause, 2 days quinine 1 gram, then every Wednesday and Saturday or Sunday 1 gram for another 6 to 8 weeks;

b. In ordinary perniciosa accordingly (after disappearance of the asexual forms or the fever) for a further 8 days 2 grams of quinine per day, then 2 days pause, 2 days quinine (1 gram) 2 days pause, 2 days quinine (1 gram), then as under *a*;

c. In quinine resisting malaria, as under b, but combined with neo-salvarsan. Once every 7 days, rising from 0·3, 0·45 to 0·6; this 6 to 8 times.

My after-treatment thus passed into my quinine prophylaxis, every Wednesday and Saturday 1 gram, as introduced as being the most efficient during the world war, by the German Army Command for all soldiers on the march.

Nocht and his followers give in malaria 1 gram of quinine during fever and daily for about 5 days after the last day of fever, the quinine being distributed over 2 hours in doses of 0·2 or 0·25 per day. Then 4 days pause, 3 days quinine, 4 days pause, 3 days quinine, etc. for about 6 to 8 weeks.

Quinine prophylaxis with divided daily doses of quinine not being practically feasible for disciplinary reasons, and as, for the same reasons, the after-treatment must correspond to the quinine prophylaxis, I decided in favour of my method of undivided doses.

In case of risk of blackwater fever and in persons sensitive to quinine, *Nocht's* method nevertheless is to be recommended.

I attach chief importance above all to the energetic treatment of pernicious malaria with 2 grams daily doses of quinine.

Further points regarding general therapy of malaria resistance to quinine: During and after the world war cases were again obser-

ved in which quinine apparently failed completely. I have divided this quinine resistance into 3 groups:

a. Occasioned by preferential location of the parasites in the capillary regions of internal organs (determined in a number of certain cases).

b. Occasioned by endogenous quinine resistance of many races of parasites in certain regions.

c. Occasioned by absence of all immunity factors, in respect to which matter I refer to my work "New Problems of malaria investigation", *Berliner Klin. Wschr.* 1920, No. 28-29. (This also contains a reference to the earlier works of *Bauer* and *Rodenwaldt*).

By every case mentioned under a. I, in principle, combine quinine treatment with the systematic application of Quinckes hot air baths, quinine (1 gram or at least ½ gram) being given 1 to 1½ hours before the hot bath, in order, by hyperaemia of the outer skin, to draw the blood from the internal organs. In this way it may be hoped that the parasites will be brought into the peripheral circulation and made more accessible to the action of quinine. I finally grew into the habit of using these hot air baths in each case of relapse. (At the same time a quantity of hot tea with lemon juice). I *advise against* the remaining *"provocatory methods"*, particularly the injection of adrenalin.

To *b. quinine be combined, as already mentioned, with Neo-salvarsan.* The latter, as is known, produces an intense paraciticidal effect in tertian, even without quinine. *Nevertheless even with ordinary tertian, I, as a matter of principle, combine quinine with Neo-salvarsan* in the manner above mentioned.

To *c.* Starting out from the clinical experience that every reduction of the internal powers reduces the curableness of malaria by quinine, I endeavour by the utmost attention to nutrition (under certain circumstances even artificial nutrition) and comfort to restore the general strength rapidly.

Anaemia is fought by iron-Elarson or Haematogen or similar preparations, and by injections of astonin, optarson, etc. *In severe anaemia and cachexy I most strongly recommend the injection or infusion of "attuned" blood.* (For technique see my monograph).

Of great importance for the cure is also an *underanged functioning of the liver* (for absorption and splitting up of the quinine). Therefore provision should be made for absolute regularity of digestion by gentle laxatives (Carlsbad salt) and above all by *high enemas* daily.

On increase of the general symptoms, when the fever attack and the quinine action coincide, the troubles and any aversion to quinine may be reduced by careful doses of *morphia.*

Against tinnitus aurium I recommend pot. brom. 1 gram 2 to 3 times a day.

In severe vomiting (frequent in perniciosa) I urgently recommend chlorofm., gum. arabic. aña 10, Sacc. 20, Av. ad. emulsionem 200, ½ to 1 tablespoonful (may be repeated 1 hour later). This treatment has now extended pretty well everywhere in the tropics.

I found no advantage from *abortive treatment* in order to cut short the infection by large doses of quinine and Neo-salvarsan or Sulphoxylsarvan, in a short time, nor yet from treatment with methylene blue.

Regarding baths and climatic therapy see also the monograph.

In conclusion it may be mentioned that in all cases where there is no absolute certainty that the quinine treatment prescribed is carried out, such treatment should be checked by examining the urine with the quinine reagent (potassium-mercury iodide, obtainable from chemists). This reagent produces turbidity or deposit in urine containing quinine which dissolves on heating but must form again after cooling.

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THE TREATMENT OF MALARIA

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IN an article in the *Journal of Tropical Medicine and Hygiene*, of Dec. 1, 1924, Vol. XXVII, No. 23, p. 321-22, the author proposes the following "improved method of giving quinine".

The amount of quinine to be taken during the first fortnight of treatment.

According to the directions given in the article, written by Dr. *Manson Bahr* for the *Lancet* of March 8, 1924, on the treatment of malaria, 30 gr. are ordered for the first seven days and 20 gr. a day for the second seven days. In my practice I give 20 gr. for the first four days, and after three days rest from quinine I give 20 gr. a day at the beginning of the second week and for three days only. I am thus giving 140 gr. against 350 gr. of the advised treatment. Now in the great majority of cases the treatment is ordered but not directly supervised, and in this connection I should like to quote the aphorism of an unknown Arab physician as recorded by Professor *E. G. Browne* in his third Fitz-Patrick lecture: "Know that I and thou and thy disease are three factors mutually antagonistic. If thou wilt side with me, not neglecting what I enjoin on thee, then shall we be two against one, and we will overcome the disease".

Put differently, we must obtain the co-operation of our patients, and we can hardly expect to do so in a case of malaria, when, as one would surmise on theoretical grounds, and one knows from numerous cases, that patients who religiously follow the *régime* on the lines laid down suffer very largely from quininism, and in many other cases give up the full doses or take to smaller amounts. There is also a considerable personal variation in the matter of the taking of quinine which should always receive consideration.

Having in view the facts as to the absorption and excretion of quinine, it is clear that of 30 gr. taken on the first day, some carry through to the second and even the third day, and the accumulation goes on at a high rate until the fourteenth day, so that quininism

would appear, as I have found it to be, usual, if not inevitable. I cannot regard it as necessary to give the drug to this extent. I do not remember it to have been looked as good practice to keep a syphilitic in a state of salivation. It must be remembered that by the fourth day the signs of the disease are not evident except perhaps for some enlargement of the spleen and some anæmia, and yet it is ordained that, as a routine, patients should swallow these large doses, although the work to be done is a diminishing factor, while the drug accumulates in the system.

The later treatment of malarial patients.

Having, as stated above, given four days of quinine followed by three days without, most of the quinine will have been excreted at the end of this period, and it may be that such malarial organisms as have survived will again begin to be active, so I then give three days quinine and follow by four days rest, and then, according to the case, I give three or four weeks of 20 gr. on three days, three or four weeks of 20 gr. on two days in the week, and finally three or four weeks of 20 gr. on one day a week. I always instruct my patients to begin to take their quinine on the same day in the week. In this way the malarial organism is kept well under control and at the same time ample opportunity is given for the resistance of the individual to have a chance of developing. By the system I use and advocate about 500 gr. of quinine are given against about 1,050 gr. by the method prescribed by *Dr. Manson Bahr.*

The treatment of relapses.

The treatment of relapses depends greatly on circumstances but speaking generally I regard a relapse as not requiring anything like as much as a primary case. Judging largely by the size of the spleen, I give a course two-thirds or one-half or even less of that given above, and in order to assist in the prevention of relapses I advise the taking of quinine whenever there is any considerable departure from the ordinary habit of life. Under these conditions I advise quinine on the first, second, eighth, and sometimes the fifteenth day. The sort of events which create or appear to create the necessity for this line of treatment are journeys, changes of climate, fatigue from any cause, etc.

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A CRITICAL CONSIDERATION OF THE TREATMENT OF THE MALARIAS

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CONSIDERATION of the treatment of the malarias will of necessity under present conditions deal first with the alkaloidal derivatives of cinchona bark, particularly with quinine.

The Alkaloids of Cinchona bark.

Roughly speaking, an acid infusion of the bark from a given species and strain of cinchona, containing the alkaloids, will in the process of manufacture be treated in one of two ways. If the bark's quinine content be not sufficiently great to permit economically of the commercial extraction of this alkaloid, the whole of the alkaloids will be precipitated therefrom by caustic soda and will be sold as *cinchona febrifuge*. According to *MacGilchrist* (1915 *a*) every batch of bark varies in alkaloidal content and cinchona febrifuge has no fixed chemical composition. *Prain* (1924), however, reports that the proportion of quinine to the other alkaloids of cinchona in the bark of a particular species grown in any locality where the conditions permit of its cultivation is remarkably constant.

If, however, the bark's quinine content be high, the sulphate is separated from the acid infusion by special means. After extraction of quinine the infusion may again by treated in one of two ways. Either the whole of the *residual alkaloids* may be precipitated by caustic soda and used for treatment under that name; or there may be extracted, one by one, first the crystalline alkaloids by precipitation (cinchonidine as a tartrate, quinidine as an acid tartrate, and cinchonine by virtue of its insolubility in 80 per cent. alcohol), then the non-crystalline as a brittle or treacly mass thrown down by the evaporation of the spirit in which they have been dissolved and known as *quinoidine* or *amorphous akaloid.*

The average analysis of Indian and Sumatran cinchona febrifuge and of Indian residual alkaloid are given as follows (*MacGilchrist*, 1915 *a; Fletcher*, 1923): —

	Cinchona febrifuge.		Residual alkaloid.
	Indian. per cent.	Javan. per cent.	Indian. per cent.
Quinine	7.4	11.5	3
Cinchonine	18.58	26.3	35
Quinidine	22.83	5	20
Cinchonidine	5.84	20	2
Quinoidine	29.12	37.2	30
Water and ash	16.23		10

Quinine.

Confident recommendations of the most successful methods for the treatment of the malarias by quinine, in varying doses of the alkaloid or of its many salts, at varying intervals and hours, are conspicuous in the pages of the *Tropical Diseases Bulletin*. Their number induces scepticism. In attempts to determine the best method of quinine administration several procedures have been or may be followed.

1. The means by which quinine exercises its beneficent effects have been investigated. Knowledge of these would enable it to be used to the best advantage.

Quinine however administered, enters the blood. *Ramsden, Lipkin & Whitley* (1918) found that after administration of quinine serum contains 2 or 3 times as much of it as do erythrocytes. *Morgenroth* (1918) and *Schilling & Boecker* (1919) found when quinine was added to defibrinated blood the red cells contained more quinine than the serum. The conditions are different and the observations not necessarily contradictory. Returning to the work of *Ramsden, Lipkin & Whitley*, within 3 minutes of injecting quinine direct into the rabbit's circulation 90 per cent. has disappeared thence. It, however, reappears: — 1. stored—slightly in lymph glands, considerably in bone marrow, and highly in kidneys, spleen and adrenals. After the intraperitoneal injection the last contains at least 700 times as much, weight for weight, as does blood. Quinine so stored is destroyed or "metabolized" by the tissues. Tested by incubating these with known quantities of quinine, its metabolism is greatest in liver, intestinal wall, muscles and kidneys. Since quinine contains merely the same elements as do hundreds of other organic bodies its metabolites can be indentified only by their constitution, not by their atomic constituents; and their constitution, identity and reactions are unknown. Metabolized quinine disappears in the body without trace in our present knowledge. 2. Quinine is expelled from the body, not at all in the faeces, unless there be diarrhoea, to a variable extent in the urine. *Hartmann & Zila* (1918) hold the percentage so excreted to vary from 15 to 35—more generally

it is placed between 23 and 65; when 90 gr. were administered daily for 2 days it lay between 7 and 11 *(Ramsden, Lipkin & Whitley,* (1918).

Quinine undergoes, then, after absorption, one of two fates. Part is ejected unchanged from the body by the kidneys, the rest, varying from 35 to 93 per cent., is broken up into unknown bodies. To which moiety is the beneficent action of quinine due? In either case is the action direct or indirect? The literature speaks uncertainly. On the one hand lie such conclusions as these: — "During that minute, however [before 90 per cent. of quinine leaves the circulation], the physician knows that the quinine is present in the circulation in maximal concentration, and that its full destructive effect is being exerted upon such parasites as have not reached the 'safe area' within the erythrocytes". On the other hand are these facts. *Bass* (1922) finds that in the cultivation in vitro of schizogonic forms of *P. falciparum* a 1 in 4,000 solution of quinine causes evident degeneration of intra-corpuscular forms within 5 hours, this quantity being equivalent to 2 grammes in the whole blood of a man of 150 lb. But, as has been noted, the rapid disappearance of quinine from the blood seems to exclude the possibility that such a concentration should ever occur there at all, certainly that it should persist for five hours. *Morgenroth* (1918), indeed, estimates the quinine content of blood as only 1 in 20,000 a few minutes after intravenous injection and 1 in 150,000 to 1 in 500,000 after oral administration. *Kirschbaum* (1923) found citrated blood containing *P. vivax* to be still infective after incubation at blood temperature for 5 to 24 hours with an equal quantity of a 1 in 5,000 solution of quinine. In eleven cases of the great Liverpool series (see below) the quinine content of the blood was estimated. In those 3 in which it was highest and quinism greatest *P. vivax* persisted longest in the peripheral blood. In one of the 3 (taking 5 gr. of quinine 3 times a day, 6 days a week for 3 weeks) the parasites never left the cutaneous circulation at all. In another *Ramsden, Lipkin & Whitley (l.c.)* found the maximum strength of the quinine to be 1 in 100,000, 27 hours after administration, in a case in which parasites persisted longer than in most cases.

The evidence suggests, then, that quinine is not specifically poisonous to plasmodia, but that it acts by producing, directly or indirectly, bodies which are. If, however, quinine act through metabolites, then, granted equal dosage and absorption, that individual in whom a large percentage of the drug is excreted unchanged in the urine is using it unsatisfactorily. We have, however, no evidence that quinine is ever completely unabsorbed or completely metabolized. Accordingly its absence from the urine may still reasonably be accepted as proof that

none has been taken, but the quantity recovered does not indicate the quantity received. Warrington *Yorke & Macfie* (1924) suggest as the most reasonable explanation of facts that quinine directly or indirectly destroys a percentage only of plasmodia, that this dissolution induces, through the freeing of antigen, the formation of immune body, and that the last, not quinine, destroys the remainder of the parasites and disinfests the host—provided the body has adequately reacted. Such considerations indicate that the mode of action of quinine is too imperfectly known to afford guidance as to its best method of administration.

2. Investigation of quinine resistance.—If quinine fail to cure malaria, and if the conditions under which such failure occurs could be discovered, the principles underlying effective treatment might well be established. *Fletcher* (1923 *a*) has indefatigably and critically investigated reputed quinine-fastness in hundreds of persons. In one only have malaria parasites persisted in the blood after he satisfied himself personally that the quinine ordered had been swallowed. *Bass* (1923), too, fails to find substantiation for claims that quinine resistance exists; and *Ravaut* and collaborators (1917) have disproved its existence in many cases in which it had been accepted. Similarly, Warrington *Yorke & Macfie* (1924) find that when quinine ordered orally has failed to eradicate parasites from the cutaneous blood intramuscular injection has invariably produced this result. There has been no quinine resistance. The drug has not been absorbed, possibly not swallowed. The investigation of quinine resistance has but attested the efficacy of quinine in ridding the blood of malaria parasites. It has thrown no light on its curative mechanism.

3. By comparing the percentage of recovery when quinine is administered in different ways attempts have been made to discover the best line of treatment. Owing to the impossibility of determining whether disinfestation has been attained, such "cure" has commonly implied freedom from clinical and parasitic relapse after treatment has ceased over a test period of arbitrarily chosen length. Owing to the significant but commonly overlooked conclusions independently reached by both, two only of the many recorded sets of experiments need here be considered—the Liverpool cases (*Stephens et al.*, 1918) and the Macedonian cases (*Anderson*, 1922).

In the Liverpool series hundreds of men were submitted between February, 1917, and May, 1918, to a number of different treatments. The test period was 8 weeks. Of the various treatments, one, 90 gr. of quinine sulphate daily in solution on each of two consecutive days, was repeated at a different season. Of 76 cases treated by it from July

to September, 29, or 38 per cent., relapsed, while of 89 treated between January and April, 83, or 93 per cent., relapsed.

The Macedonian experiment was carried out under conditions of locality and control which also reasonably excluded reinfection. Using the same sets of quinine treatments on 199 cases, 92 admitted before July 1st and 107 from that date onwards, the percentages of relapse for each treatment were respectively 72, 71·4, 68·1 and 70·8 for the first period and 28·5, 35·1, 36·3 and 17·6 for the second. Of 17 controls 76·4 per cent. relapsed in the earlier period and of 27 controls 62·9 per cent. in the later. Similarly massing together the Liverpool experiments the percentages of relapse for the four quarters of the year were 96·7, 78·3, 36·5 and 64·8. The Liverpool workers did not conclude that "nice warm weather is a better cure for malaria than quinine", but held that on the evidence season has a great influence on the efficacy of quinine treatment of malaria in the class of case concerned (an influence difficult to dispute after the Macedonian confirmation), and that it is at least clear that to attempt to determine the value of a line of treatment merely by noting the number of relapses which follow it within a particular time is useless. This conclusion renders meaningless most of the vast mass of work upon which the relative values of various quinine treatments are estimated. A seasonal efficacy of treatment correlating itself with the recognized seasonal tendency to relapse is not unreasonable.

4. The stage of infection—clinical or pathological, not biological—at which quinine treatment is instituted requires notice. It has been urged by *Génévrier* (1921) that malaria, like syphilis, has three stages: (i) before gametes appear, lasting 10-12 days; (ii) the intermediate condition; (iii) after visceral lesions establish themselves. The reasonableness of such division is combated by *Ed. Sergent* (1921). Experience on the continent of the treatment of benign tertian malaria, deliberately induced by injection for the amelioration of general paralysis, shows that these first attacks are almost invariably cured with 5 gm. (75 gr.) of quinine sulphate. Warrington *Yorke & Macfie* (1924) have confirmed these findings in a considerable series of cases—mosquito-carried as well as injected—closely followed up. They used 6 gm. in all, namely 30 grains on three consecutive days, with a relapse percentage of 1·6 in injected and 13 in mosquito cases. Moreover, a number of paralytics have died at various periods after treatment of induced malaria. In none has close search of the organs detected plasmodia. *Seguin's* experience of ordinarily acquired malaria convinces him (1921, 1922) that recent infections are essentially curable. Such experiences, in their marked contrast to those of Macedonia and East

Africa in war time, indicate another factor of a vital nature and yet one generally, perhaps completely, disregarded in comparative statistics.

5. The best route, time, medium and interval of administration and the best salt have been canvassed. By reason of the millions of persons involved the *oral route* must ordinarily be employed. Its efficacy is amply evidenced, *e.g.*, by *Collett* (1920), but the immense majority of cases are of course not published. One reason of its apparent failure *Fletcher's* work has, as noted, indicated. It has been suggested that its administration in tablet form is another. It has, however, been shown that properly made tablets of quinine hydrochloride produce at least as much urinary excretion of the base as does the same quantity in solution, (*Seidelin*, 1922). There has been a tendency to blame sugar coating as preventing absorption (*Langeron*, 1922), but sugar cannot but rapidly dissolve in any aqueous fluid. The fault really lies in the tablet's menstruum, which, as *Blanchard* has shown (1922), may resist solubility for months and defy the attack of a hammer. It is as useless to expect absorption by solution of the quinine which lies in the centre of an impervious lump of concrete as it is unreasonable to condemn the popular, sugar coated, rapidly disintegrating tablets of proved efficacy, and yet the quality of the menstruum is rarely considered in the reports of the cases; a state of things which perhaps prompts the generally recognized advantage of solution over quinine in tablet form. *Munk* (1917), *Mariani* (1904), and *Giemsa & Schaumann* (1907) conclude from urine analysis that the less soluble salts of quinine are absorbed from the gastro-intestinal canal at least as energetically as the more soluble. *MacGilchrist* (1911), finding the maximum elimination of quinine taken fasting to be 3 to 6 hours, and taken with food 6 to 12 hours, and correlating this with a maximum gastric retention of food for 5 hours after administration, concludes that absorption is mainly from the small intestine, and that quinine, as whatever salt given, has, before absorption, been necessarily precipitated as the alkaloid by the alkaline intestinal juices. Intestinal solution and absorption, one presumes, would accordingly depend on the fineness of the resulting precipitate. On the relation of food to quinine absorption *Ross* writes (1910, p. 136): "I have observed in experiments on myself that quinine taken just before a meal causes *tinnitus aurium* in about half-an-hour, this proving its rapid absorption; but taken after a meal it does not produce this effect so quickly."

There is a widely held inference (*cf. Hay-Michel*, 1918; *Michael*, 1920; *McCarrison & Cornwall*, 1919) that quinine is only effective during sporulation, that is to say, against extra-corpuscular stages,

among which sporozoits, too, are apparently to be included, *Cardamatis* (1918) urging that quinine should be begun 7 or 8 hours before the paroxysm is due. Evidence has not been traced in its support. On the contrary, *Rieux* (1918) observes that if quinine administration be started when schizonts are very young, growth ceases and degeneration begins. If started when these are half grown, some are killed and degenerate and some carry on to sporulation. If begun during sporulation this is not checked. In gametes change is less rapid but degeneration follows in time. Possibly the inference mentioned is an illegitimative offspring of the belief that quinine is not absorbed by erythrocytes. As noted, *Bass* finds that quinine in a concentration of 1 in 4,000 produces degeneration of intracorpuscular forms. The giving of quinine at a special phase of the life cycle does not appear, then, to be based on scientific observations.

For *intramuscular injection* of quinine the small bulk of fluid available renders necessary the use of a soluble salt, the bihydrochloride being commonly used. The true value of this route remains undetermined. In *MacGilchrist's* experiments with bihydrochloride (1911) necrosis followed intramuscular injection into guineapigs so rapidly as to exclude even thrombosis as its cause. It was widespread in dilutions as weak as 1 in 150 and quinine was precipitated in and recovered from the necrotic tissues. The experiments of *Dudgeon* (1919) leave no doubt on this matter, and *Hele* (1922) reports the same finding. *Mariani*, too *(l.c.)*, found 60 per cent. of quinine bihydrochloride in rabbits' muscle 17 hours after its injection. Clinically, too, the sequelae of intramuscular injection can be grave or catastrophic. Apart from the reappearance in the literature of deaths from tetanus (*Borel & Maire*, 1923), sterile injections may be followed by wide necrosis of muscle, nerve and artery (*Ross*, 1914; *Fletcher & Visuvalingham*, 1922-23; *Acton & Knowles*, 1924; *Basset-Smith*, 1923; and many others), and may be so painful that further experiences in that direction are refused.

On the other hand, *Lipkin* (1919), using apparently the bihydrochloride, found that no unusual appearances were exhibited at the site of injection, and that quinine seemingly rapidly disappeared thence. With his finding is presumably to be correlated the widely expressed experience (*Clarke*, 1914; *Clarenc*, 1913; *Fox*, 1917; *Simpson-Wells*, 1917) that when oral quinine fails an intramuscular injection may result in disappearance of parasites from the cutaneous blood, after attaining which oral quinine may beneficially be resumed. *McLay* (1922) has compared films taken after giving 60 grains of quinine bihydrochloride (a) by mouth, (b) intramuscularly or subcutaneously,

and found that they became negative earlier with oral administration. The conditions under which intramuscularly injected quinine will produce widespread necrosis, with its terrible sequelae and without rapid absorption as distinguished from those under which the reserve seemingly holds are not determinable on existing data. *Mathieu* (1922) points out that these grave potentialities for harm inherent in intramuscular injection preclude in fairness the delegation of these injections to subordinates, while the uncertainties regarding absorption exclude this route where rapid effect is essential.

There is no evidence that disinfestation is more readily obtained with intravenous than with oral quinine, but where rapid access of quinine to the blood stream is imperative, as in coma or the antecedent hyperparasitism, *intravenous medication* is very strongly advocated (*Griffin*, 1917; *Willcox*, 1920; and many others). *Brahmachari* (1922), to avoid the fall in blood pressure which has accompanied some of his injections, dilutes ten grains of quinine, presumably bihydrochloride, with not more than 200 cc. of normal saline, administration occupying 20 minutes. Others merely advocate slow injection, which seems to attain the same object so far as dilution in the circulation goes, although any leakage beside the vein will be of concentrated solution with its attendant risk of necrosis. If intravenous injection can be accomplished with tartar emetic for kala azar by Indian subassistant surgeons at the rate of 3 or 4 cases a minute (McCombie *Young*, 1924), a medical man with European training has little justification for its disregard with quinine in malaria at his leisure, on the ground that it is a skilled operation.

While the risk of local damage by *rectal quinine* is such, in *Fletcher's* experience (1923 *b*), as to prelude its use, *Newham* (1923) and *de Freitas* (1923) reaffirm its value and certainty in overcoming acute malaria.

6. Another variable constantly overlooked lies in the species of parasite concerned. For quartan malaria quinine has been reported as giving unsatisfactory disinfestation (*e.g.*, *Leslie*, 1923). In *MacGilchrist's* "minimum therapeutic dosage" experiments (1915 *b*) he found that to remove asexual parasites from the peripheral blood there was required for benign tertian malaria 0.1 gm. of quinine per 70 kilo body weight, the dosage for malignant tertian malaria being 0.15 and for quartan malaria 0.2 gm. The cases were few. No evidence seems to exist that the minimum therapeutic dose and the disinfestant value run parallel. As already noted (see *Tropical Diseases Bulletin*, Vol. 20, p. 777), *Wenyon* (1921), *Mayne* (1920), and *Walch & Walch-Sorgdrager* (1921) have produced evidence that quinine is more potent

against the schizonts of *P. falciparum* than of *P. vivax*, whereas for the gametocytes the condition is reversed; *Muehlens & Kirschbaum*, too (1921), have infected *A. maculipennis* with blood containing crescents, the donor being quininized. Evidence then accumulates that not merely biologically and symptomatically but therapeutically there are three malarias, and that the last aspect requires wider realization and investigation than it has hitherto received in estimating the therapeutic value of quinine.

Conclusions.

It does not seem possible, from these considerations, to avoid inferring that by reason of our ignorance regarding the intracorporeal reactions of quinine, of loose talk concerning quinine resistance, of the discovery that in all likelihood season affects the therapeutic efficacy of quinine, of lack of knowledge of the factors making for ready absorption of quinine from alimentary canal or muscle, and of failure to take into consideration that the action of quinine differs in early and late cases, in the different stages of development, and in the different species of plasmodium, our knowledge forms no scientific basis for determining the best line of treatment with this valuable drug, and, indeed, gives no indication as to whether such special modifications of administrations as have been strongly advocated really serve any useful purpose.

A few lines of treatment are, however, at present favoured: —

1. The Standard Treatment of the United States National Malaria Commission specially advocated by *Bass* (1921). Thirty grains (2 gm.) daily of quinine sulphate so long as clinical symptoms continue, or for 3 or 4 days, in 3 doses of 10 grains each, and thereafter 10 grains daily for 8 weeks, this course being held to disinfect 90 per cent. of cases.

2. *Nocht's* Treatment.—1 gramme daily of the bisultphate in powder in fractional doses of 0·2 gramme two-hourly from 6 a.m. to 2 p.m., for ten days continuously, and thereafter, with certain intervals, for two months.

3. *Ross's* Treatment.—A ten weeks' course entailing administration of 15 grains of quinine sulphate or hydrochloride daily for 2 weeks and thereafter 10 grains daily on 6 days a week for 8 weeks—a total of 690 grains.

The common feature of all these treatments is the prolongation of the course. *Acton* and collaborators (1921) have shown that in relapses of benign tertian malaria a given quinine treatment—those tested ranged from 300 to 1,980 grains—will cure a definite percentage of cases, and its repetition will cure the same percentage of the relapsing,

8 weeks being taken as the test for cure. *Ross* (1921) points out that a similar fractional curative effect follows each dose—the Single Dose Reduction Rate.

No evidence has been traced in favour of the widely expressed inference that provocatives which cause reappearance of plasmodia in the cutaneous circulation aid in any way the action of quinine.

Cinchona Alkaloids other than Quinine.

There is considerable evidence that the general disregard of cinchona alkaloids other than quinine is therapeutically unjustified and economically unfortunate. *MacGilchrist* (1915, *b*), working in Calcutta from September to December, determined on 113 prisoners the weight in grammes of the various alkaloids required to produce a negative blood examination, presumably in a thin film. Dosage was at the rate of 1 gramme per 70 kilos. body weight at each of 3 doses daily, a blood film being taken at the time of every dose. For quinine, cinchonine, quinidine and cinchonidine the respective average figures were for benign tertian malaria 4·7, 5·5, 5, and 5·6 grammes, and for sub-tertian malaria 6·1, 5·6, 4·85 and 4·3 grammes. In this series quinine acted most rapidly upon *Plasmodium vivax*, cinchonidine upon *P. falciparum*. It would not necessarily follow that their capacity for complete disinfestation would lie in the same order. Judging by the minimum therapeutic dose (see p. 85), the relative curative values for the cinchona derivatives were, without distinction of the two parasites, first hydroquinine hydrochloride, next, and of practically equal value, the sulphates of cinchonine, quinine and quinidine, then, in order, optochin hydrochloride (ethyl-hydro-cuprein), cinchonidine sulphate, and, lastly, quinoidine. *Acton* holds (1920) that the laevo-rotatory quinine and hydroquinine are specific for *P. falciparum*, whilst the dextro-rotatory quinidine acts more powerfully on *P. vivax*. He puts the cure rate of the cinchona alkaloids for *P. vivax* as—quinine 20 per cent., cinchonine 40 per cent., cinchona febrifuge 50 per cent., cinchonidine and quinidine 60 per cent., and quinoidine 0. *Rogers* (1918) finds that in rabbits cinchonine is absorbed after intramusclar injection more completely than is quinine; and that in man its use is less painful and causes more rapid disappearance of plasmodia than does quinine. *Bini* (1921) advocates cinchonine, *Silvestri* (1923) reports a few experiments in which cinchonine bihydrochloride injected intramuscalarly gave less local precipitation and greater visceral accumulation of the drug than did the corresponding quinine salt, while in oral administration more of the former was excreted by the urine than of the latter. *Cordes* (1924) finds cinchonine less satisfactory for subtertian malaria

than quinine. Quinoidine, in opposition to the conclusions of *Acton* (see above), in daily doses of 6 grains (*Waters*, 1916), 9 to 18 gr. (*Telang*, 1916), 12 grains (*Razzak*, 1917), is recommended as equal in action to quinine. *Row* (1919) found quinoidine incapable of eradicating the parasites or preventing relapses. The contradictory evidence suggests that quinoidine varies in composition and that some of the amorphous alkaloids are valuable, others worthless.

It is of no little economic importance that further investigation, taking cognizance of the sources of error above mentioned, should put the relative value of the cinchona alkaloids on a satisfactory footing.

Other lines of treatment.

Neosalvarsan, so far from being curative in subtertian malaria, has been in a number of cases the cause of death, lighting up a malaria latent and recognized too late. On benign tertian malaria its immediate effect in suppressing parasites is generally marked, yet relapse has constantly been reported. Mercury and tartar emetic have failed. Splenectomy does not disinfest—may indeed induce immediate and fatal relapse (*Degorce*, 1913). X rays, used under certain precise conditions (*Pais*, 1923), are still advocated as curative. The good results reported with infusion of *Vitex peduncularis* by *Vaughan* (1921) have not been obtained by *Chopra, Knowles & Gupta* (1924). The harmala alkaloids (*Gunn & Marshall*, 1919-1920) have proved valueless.

In spite of their imperfections—perhaps the result of our ignorance of their proper use—quinine and its allies remain invaluable and unsurpassed in the treatment of the malarias.

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THE RESISTANCE OF MALARIA TO QUININ

Editorial of The Journal of the American Medical Association, Chicago, Ill.

IN 1917, reports began to appear that English soldiers in the tropics were being attacked by malaria that quinin would not cure. *Pratt-Johnson* and *Gilchrist* found that relapses were reported in 23 per cent. of 18,000 soldiers in Africa while quinin was being administered; *Phear* reported in Macedonia that quinin was ineffective in malaria that was complicated by dysentery; *Willcox* in Mesopotamia encountered cases that did not improve under quinin by mouth for ten days; *Mackie* found quinin ineffective in malaria in northern Persia, and the accumulation of invalids in Saloniki was constantly increasing. Such contradiction and disappointment concerning quinin led to an extensive experimental and clinical inquiry into the treatment of malaria at the Liverpool School of Tropical Medicine, the results of which, unfortunately, did not entirely restore confidence in quinin.

Many soldiers were sent back to England from Macedonia in 1918, and *Sir Ronald Ross* arranged to treat the malaria patients in special wards at Southampton. In recently published notes, *Fletcher*[1] says that 1,150 patients were admitted to these wards in twelve months, and that on landing parasites were found in the peripheral blood in 487. Although many had documentary evidence of treatment with quinin in various hospitals, they were placed on 10 grains of quinin by mouth twice a day. There was strict supervision of these patients, and special interest in relapses that might occur. In every instance the routine treatment prescribed at Southampton caused both fever and parasites to disappear.

Fletcher emphasizes the Southampton experience by a report of his observations in the Federated Malay States since the war. The patients seen there were little more than skeletons, and dysentery was a complication in 53 per cent. Forty-four difficult cases in which quinin had been disappointing were selected, and 10 grains (0.65 gm.) of quinin by mouth twice a day was given for four weeks. The drug was placed in the patient's mouth by the physician, and, after it had

1. Fletcher, William: Notes on the Treatment of Malaria with the Alkaloids of Cinchona, London, John Bale, Sons & Danielson, Ltd., 1923.

been swallowed, the mouth was inspected. Not one of these coolies in Kuala Lumpur failed to improve. There was in one a small number of parasites that persisted in the blood in spite of quinin, but in every other case, both fever and parasites disappeared. Dysentery did not make any difference. When quinin was actually swallowed and retained, malaria in dysentery patients was as easily controlled as in patients who did not have dysentery. The conclusion of this study was the same as among soldiers in Southampton: that the so-called resistance to quinin vanished when the quinin was actually swallowed and retained.

The obvious alternative would seem to be to resort to injections. Intramuscular injections of quinin were used extensively in the campaign in Macedonia, and this practice was subjected to inquiry. It was demonstrated experimentally that whatever concentration or whatever salt was injected, there was necrosis of the muscle at the site of injection. Large nerves may be involved with paralysis, and abscesses may form. *Sir Patrick Manson* opposed intramuscular injections unless made for good reasons. *Sir Ronald Ross* has repeatedly expressed his opposition in ordinary cases. It is not generally recognized that intramuscular injections of quinin always cause necrosis, or that quinin is absorbed more quickly by mouth. *Fletcher* in Kuala Lumpur injected 10 grains of the dihydrochlorid in 22 minims of salt solution into each buttock of twenty-two patients. The shortest time in which quinin appeared in the urine of any patient was twenty minutes, and the average time was sixty minutes. The same amount of the same salt was given by mouth to a similar group of patients, and the shortest time in which quinin appeared in the urine of any patient was less than fifteen minutes, and the average time thirty-one minutes.

There is a profound fall in blood pressure when quinin is introduced intravenously, which seriously affects the respiratory center. *Fletcher* has seen one death and one case of serious illness due to sepsis after intravenous quinin injections. In a clinical investigation of rectal injections he concluded that quinin is too irritating to be administered in that manner.

In general, *Fletcher's* report is a plea for the restoration of faith in quinin in malaria, and for its oral administration. He does not say that an absolute resistance to quinin is impossible, but in a wide experience he has not seen one case of actual resistance.

(*Journal of the American Medical Association,* Chicago, Ill., **82:** Nr. 14, April 5, 1924, p. 1125)

ON THE TREATMENT OF MALARIA BY INTRAVENOUS INJECTIONS OF QUININE

(UEBER DIE BEHANDLUNG DER MALARIA MIT INTRAVENÖSEN CHININININJEKTIONEN)

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THE writer, on the strength of the good results obtained by Dr. *Dobrotin* with intravenous quinine injections against malaria, himself applied this treatment in such manner that control was possible for one year after the treatment.

We treated 224 patients receiving 1703 injections:

Mal. tertiana	137 cases	771 injections
Mal. tropica	60 „	624 „
Mal. quartana	7 „	95 „
Mixed infections	20 „	213 „

After microscopical determination of the diagnosis, on the first day usually 6 c.c. of a 10 % solution of bihydrochloride of quinine, was injected into a vein. A day later, according to the strength of the reaction, 8 to 10 c.c., and on the third day 10 to 12 c.c., even 15 c.c. In one particular case 10 c.c. of a 20 % solution was injected once.

In tertian malaria the injections were made 4 to 5 days in succession. As relapses occurred speedily the first series of injections was followed by a second series of 4 to 5 injections. Sometimes a week later there were one or two treatments consisting in quinine for 4 days per os.

Fifty cases thus treated gave:

1st series	36 patients;	28 relapses,	8 no relapse
2nd „	12 „	11 „	1 „ „
3rd „	1 patient;	1 relapse	
4th „	1 „	1 „	

Therefore 82 % relapses and 18 % no relapses.

Among these patients 37 were chronic and 13 acute malaria. In the chronic, 81 % relapses, in the acute 84 %. Treatment by several series therefore gives no better results, while in acute and chronic cases it produces the same results.

It is interesting to keep the patients under observation for a fair time. In 271 to 300 days after the treatment 82 % of relapses occurred. It was also found that tertian malaria strongly tends to relapse in the spring and summer. Less so in the winter.

Patients with tropical malaria were given the same quantity as the tertian group, except a couple of cases which had two injections per day. Mostly the injections were given for 7 days, after which one week's interval. After a couple of weeks, every three days, 4 days injection treatment and when the blood was free from parasites, 2 further series.

On a few occasions quinine was replaced by methylene blue, 0,5 to 1 gram per day.

Eighteen patients who received quinine exclusively gave 72 % relapses. Fourteen patients who received quinine and methylene blue, showed 57 % relapses. As however the last group received more quinine than the first, the favourable results may not be attributed to the methylene blue.

From all this it follows that the opinion of *Dobrotin* that 9 injections cause the disappearance of the tropical form is incorrect, because a large percentage relapse.

The treatment of the quartan (7 cases) yields the same results.

As complications of the intravenous injections the writer mentions, inter alia, that repeated injections result in an aseptic thrombo-phlebitis. In 1703 injections he found, in two cases, an abscess, and in 4, disturbance of consciousness (20 to 30 seconds).

A comparison between the preventive effect of intravenous injections, as compared with quinine per os, shows that on the average 1.28 gram of quinine intravenously prevented an expected attack in 85 % of the cases, while, per os, with an average of 2.32 gram this percentage was 64 %. The writer concludes that intravenous injection may be considered where the point is to cut short the attacks as speedily as possible.

It is indicated in comatose conditions and also perhaps in those cases in which administration through the mouth causes obstinate vomiting.

(*Archiv für Schiffs- & Tropen-Hygiene*, Leipzig, **28**: N. 11, Nov. 1924, p. 488-495. Summarized)

INTRAVENOUS INJECTIONS OF QUININE AS TREATMENT FOR CHRONIC MALARIA

(LES INJECTIONS INTRAVEINEUSES DE QUININE COMME TRAITEMENT DU PALUDISME CHRONIQUE)

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DURING the colonial campaigns of the last third of the XIXth century, medical officers observed forms of intense and acute malarial infection, which necessitated the absorption by the sufferers of large doses of quinine and quinquina.

Habituation to these forms and doses died away, because, both in our distant colonies and in Algeria, malaria control measures, the improved hygienic conditions of towns, the use of quinine as a preventive, and the early treatment of every attack of fever, were factors which, in conjunction with the termination of the military operations with European troops in regions with a high malarial index, had made cases of malaria more rare and had reduced to a very large extent the density among Europeans of the parasitic infection which chiefly assumed the remittent bilious form.

Therefore, while there was a gradual fall off in the dose, intramuscular administration at the same time became necessary, owing to the bad condition of the digestive apparatus in this form.

The extended provision of medical aid for natives had, at the beginning of the XXth century, led to general contact between medical men in the colonies and in North Africa with malarial sufferers who had, from birth, been infested in a very intense form with hematozoa during a great portion of the year, or in many places even without interruption, and for whom there could be no question of a change of habitat.

The treatment of malaria by quinine therefore was trending, before the war, in the direction of restoration of considerable doses and renewed utilisation of quinquina.

The war in Morocco, in the East and in the Cameroons again placed European troops in conditions comparable to those of the conquest of Algeria or the first colonial campaigns, and patients

similar to those of the old expeditions were observed. For their treatment the doctors again had to have recourse to the heavy doses of quinine, of which they had lost the habit. The intravenous method, the use of which was more recent, but which had also been greatly neglected, came into vogue again with the frequency of pernicious attacks.

This method, which had only been employed before the war by medical men here and there, because they alone observed the pernicious forms of malaria, became generalised in the French colonies, among doctors of the brushwood areas, towards 1903, at the time of translation into French of *Manson's* book. The terms: "Bacelli injections" and "malarial chill" remained, to them, almost inseparable.

In the army of the East the method was extended to all recent forms of malaria. *C. Hartmann*[1] has, by a complete study of the question shown extension of the method, *the object of which is to convey the largest quantity of quinine as rapidly as possible to, and keep it as long as possible at the place where the parasites and their permanent forms are found.*

Carnot and *de Kerdrel* had never, in the treatment of acute malaria by the intravenous method, observed any trouble, *hardly a little malaise and vomiting. Lapin* had already stated: *"With intravenous injections I have never observed, I do not say accidents, but even incidents"*.

C. Hartmann confirmed the harmlessness of the method. *Wyat*[2] recorded the good results obtained with it in the American Navy; *John Thomson*[2] showed that by this method the largest possible quantity of active quinine was utilised; *John Clarck* of Memphis and *S. P. James*[3] also proved how favourable this course was. *A. Nicolatra*[4] said that by its use the maximum effect was obtained.

Charles Richet junior and *Griffin, Henri Soulié* and *Job and Hirtzmann*[5], *C.-M. Wenyon*[6], *H.-M. Woodcock*[7], though advocates of the method, reserved it for certain forms of pernicious attacks.

The most obvious advantage of the vascular method is the instantaneous character of the action of quinine, which acts directly on the blood containing the hematozoon[8] and which is only eliminated after having acted on the parasites.

Opinions are pretty well divided as to the rapidity of elimination.

According to *Jeanselme and Dalimier*[9] its period of elimination is much shorter than on the intramuscular method, in which its action lasts 50 hours, but is not appreciably quicker than through the digestive passages, in which elimination is completed in 30 hours.

Laveran[10], along with *Grall and Marchoux*, held the view that the product *when injected into the vein is rapidly eliminated, so that the action of the drug, though rapid, is very brief.*

But *Riou*[11] proved that, whatever the mode of introduction of quinine, the method of elimination remains practically the same. These are likewise the conclusions of *Porak*[12]. And *Charles Hartmann* concluded that *the excretion feared by certain writers does not exist.*

It is beyond dispute that the condition of the digestive passages is often an absolute hindrance to the administration of quinine internally.

Intramuscular treatment, when it does not produce abcesses, neuritis and all the grave local troubles which have so repeatedly been urged against it, is always a very painful method. Though the application of asepsis rules to the operator and the patient, the sterilisation of the injection apparatus and the solution, a knowledge of the nerve tracts, and a judicious selection of the points of injection may obviate all the unfortunate drawbacks which have been described at such great length, it cannot be denied that this method produces severe and very lengthy suffering and if prolonged, occasions impotence of very lengthy duration.

The intravenous route requires a doctor for its use. It needs this doctor to be practised and careful. It demands complete sterilisation of the solution to be injected and of the injecting apparatus. If the quinine is used in a concentrated solution its use may induce obstructing phlebitis, but there is nothing which renders the use of high concentration obligatory.

Carnot and de Kerdrel used a solution of 2 per cent.; *Richet and Griffin* a more diluted solution, *Jeanselme and Hanaud* diluted the alcaloid to 1 per cent., *R. Lafond* to 8 per 1000, *Garin* to 5·60 per 1000, *Barbery*[13] to 4 per 1000, and it is certain, as pointed out by *Brahmachari*[14], that this degree of dilution may be still further increased with advantage. By using a diluted solution, all hardening of the veins will be avoided, but there must be no hesitation if a first injection discloses peculair susceptibility of the wall of the vein, in following the other injections by an ample washing of the vein with artificial serum.

This will prevent any injurious action on the vein. There is no unfavourable alteration of the blood to be feared. *Soulié*[15] investigated, both alone and along with *Gutman, the modifications of the globular resistance after the injection of quinine. The resistance was not appreciably altered. Sometimes even it was increased. Dupérié and Obrenovitch* likewise observed no appreciable action on fragility or resistance of the globules. In *Netter's*[17] view, quinine treatment by the intravenous method increases this resistance.

The action of quinine by intravenous injection may be injurious to the heart. *Brahmachari*[18] found that the arterial pressure may fall after this injection and that serious accidents may thus be occasioned: collapse, syncope and even death. *Grall*[19], *Hetch*[20], *Matko*[21], *Laveran*[22], *Rogers*[23], *Maxcy*[24] have indicated numerous mishaps of this kind.

Other accidents, such as erythema, have been called attention to by *Patrick*[25] after intravenous injections of quinine. *Kouchev* of Saratoff also pointed to skin troubles in relation with the quinine indiosyncrasy, one case of which terminated in death immediately after intravenous injection of quinine.

"*The intravenous method*" *Abrami*[26] could say, "*which theoretically represents the ideal course, must be dismissed in practice... It frequently induces phenomena of hypothermic shock, sometimes followed by collapse, which made us abandon its use*", and *Laveran*[27] concluded a discussion at the Society of Exotic Pathology by saying: "*Intravenous injections of quinine were generalised in the army of the East in the hope that this mode of action of quinine would give more rapid and reliable results. This hope was disappointed*".

Widal, Brissaud and Abrami[28] had indeed already pointed to the danger of the injection of any heterogeneous substance into the veins: "*Death by collapse, due to algidity is a threat, the possibility of realisation of which should counsel extreme prudence in the practice of intravenous injections*".

Therefore, as *Porack* so well says: "*The intravenous method is only essential in pernicious forms, because in this case the washing of the blood vessels plays a very important part and must be added to the action of the quinine*". In many instances indeed the injection of artifical serum and serum with adrenalin have given unexpected results in the treatment of pernicious attacks.

Many writers however persist in declaring the method of quinine injection by the intravenous route the most reliable mode of attacking acute malaria[29], above all in all comatose, delirious, hypothermic, syncopic and adynamic forms with high densities of the parasite[30], with the qualification by the majority of them that this method must, in accordance with the indications of *Castellani* and *Chalmers*, be reserved for very serious cases and not be utilised otherwise than with the precautions indicated by *Brahmachari*, the method per os remaining, as is rightly and with unflagging persistency, pointed out by *Seguin*, the most convenient method, if sufficient doses are used, for treating the ordinary forms of acute malaria, which is an *essentially curable disease*.

Doctors attending natives in our distant or North African colonies

see some very peculiar malarial subjects. These are patients who have been infested from their earliest childhood with dense masses of hematozoa and who have from the outset of their existence a greatly enlarged malarial spleen, the infestation of whom has continued throughout their life either intermittently in those countries which have a winter, or, as in certain tropical regions, throughout the twelve months of the year, though with more or less intensity. And there can be no question of advising an entire population to change its country. Hygienists and prevention specialists are already securing results in preventing this continuous malarial infection of an entire population, but the practising doctor resorted to for treatment, must try to cure it. The spleen and liver of these people in particular must be acted upon. Now quinine administered by the mouth gives very little result with them. Quinquina, from which more pronounced success may perhaps be expected, is very slow in operation and cinchonine likewise is not rapid in effect.

It is an exceedingly difficult point to determine exactly the quantity of quinine fixed by the liver and the spleen of man, according to the methods of administration, because the conditions of a test in which the percentage of quinine in the blood of the portal vein and the hepatic artery would be determined on the one hand, and on the other hand, that of the superhepatic veins and the splenic artery and vein, are exceedingly difficult to combine.

The percentage of quinine in the spleen and liver is also exceedingly difficult to determine, above all for the first named organ, because the washing of the organ may remove large quantities of quinine, and on the other hand, though the largest route of excretion is the kidney, all secretions, particularly bile and all the digestive juices participate in this elimination.[31]

Until such time as these difficult tests can be carried out, we may take our stand by the works of *Grower*[32] and those of *Plehn and Rosa*[33], from which it may be concluded that quinine is fixed by all the vascular glands, and above all, by the endothelial lining of the capillaries and consequently, as regards the spleen, by all the cells of the Malpighian corpuscles. It therefore seems logical to try, by means of quinine applied intravenously, to combat the chronic forms of malarial fever in the tropics, where splenic enlargement is the characteristic lesion, where hematozoa abound in the spleen and where, according to *Léger*[34], they may still be living in a more sluggish form of life when the examinations of the blood remain negative.

P. Lafosse treated cachectic malarial sufferers in this way and obtained very good results, and *Stories-Dusson*[35] is of opinion that

the best treatment in severe cases of chronic malaria consists in intravenous injections.

The digestive passages seem to convey the quinine above all to the liver, where it stays and apparently becomes fixed in a fairly large quantity.

But chronic malarial lesions of the liver are generally secondary to a derangement of the spleen and it is to the latter organ that a large dose of quinine must be conveyed.

Impelled by these considerations I methodically applied the quinine treatment on the intravenous method during one year at Cantho (Cochin-China) in 1922-23, to a large number of chronic malarial patients presenting sclerous lesions of the spleen and the liver, with the assistance of *M. Dong-Ngoc-Dieu*, auxiliary medical officer of the Indo-China Medical Aid Organisation.

Effective intravenous quinine treatment is very trying. It is therefore desirable to prepare the patients who are to undergo to carefully and at great length. The ascites, if any, must be emptied out. The patients must be put on a severe diet for disintoxication; the hypertrophy of the spleen must be treated with atropine. *Per os* they will be subjected to severe treatment with heavy doses of quinine and quinquina until all hematozoa have disappeared from the peripheral circulation.

Then they will be given energetic anti-hemoclastic treatment with calcium chloride and lactate of strontium.

The start of quinine treatment through the veins must be made in reduced doses (for instance 0.004 gram per kg. of weight of patient) which will be progressively increased until the normal dose of 0.025 gram per kilogramme is reached. It is in no way desirable to use much more than 500 cubic centimetres of serum for diluting the quinine. This quantity of solution however is necessary in order not to injure the tunics of the veins and to allow of a long drawn out injection, lasting 15 to 25 minutes. The liquid must be hot (38°C.). The most convenient apparatus is a bottle with a syphon and rubber tube of sufficient length to prevent the needle being drawn by the tube. The flow must be regulated by the height of the apparatus, so that the entrance of air into the bottle and consequently the entrance of the diluted quinine into the veins should only take place in small bubbles and by the effect of the thoracic induction of inspiration. This produces the minimum reaction. In order to tone the latter down 0.25 gram to 0.60 gram of caffeine may usefully be added to the serum.

More diluted solutions, the different hypertonic or isotonic sera

and sweetened sera are excipients which in no way reduce the reaction. Adrenalin is also without effect.

Nevertheless, it would be extremely useful to do away with or reduce this reaction, as it is the only drawback to the method; it is however so great that frequently the patients, though persuaded of the efficacy of the treatment by striking examples in their own family, have preferred to renounce cure rather than continue a therapy, the application of which inspired them with terror.

Since so many qualified authors, whom I have cited, say so, it must be believed that quinine injected into the veins produces no reaction in primary malaria. In chronic malaria however with cirrhosis of the splanchnic organs, it is always very violent and excruciatingly painful, but happily, we may add, never grave when the precautionary measures enumerated above have been taken.

This reaction consists in excessive elevations of the temperature, violent and prolonged shiverings, in horrible sensations of chill, frightfully persistent nausea, terrible headaches, intolerable curvatures, poignant sensation of syncope and even collapse by algidity.

It must in truth be stated that all these torments are quite transitory, leave no impotence and do not, if the necessary precautions have been taken, produce any mishaps.

Collobiase of quinine[36] also given by intravenous injections, produces the same painful sensations as quinine with serum.

Subsequent intravenous injections of quinine will be guided by the indications of the first reaction and the successive crisis on each fresh injection. The patient is cured when an injection in normal dose of 0·025 gram to 0·05 gram per kilogramme of weight produces no further disturbance.

Indeed, it has been proposed as a test of the complete destruction of the hematozoa in the organism, to effect intravenous injection of distilled water, which should produce no reaction if the organism is free of all malarial parasites.

However the case may be, on reaching this point of the treatment, it will be found that the liver has resumed its normal size, that the spleen is reduced, that the proportion of leucocytes has come back to the normal and that the formula of lobulation of the nuclei of the polynuclear ones has been rectified.

The treatment, if painful, has produced a result, and such a result that the patient, when cured, never regrets having submitted himself to a course which inflicted on him a real, but transitory, martyrdom, but which, in return, has freed him from lesions against which no other method has ever had any comparable action.

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(*Paris Médical,* 26 juillet 1924, p. 88-92)

PRELIMINARY OBSERVATIONS ON THE TREATMENT OF 1,314 CASES OF MALARIA BY THE INTRAVENOUS INJECTIONS OF QUININE

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KHARTOUM is situated just north of the 15th parallel of latitude north, and has a rainfall which occurs during the months of July, August and September. The average fall is 148 mm. per annum.

In normal years Khartoum is comparatively free from malaria and completely so as regards the British population.

During 1922 the rainfall was exceptionally heavy, and totalled 366 mm., made up as follows: July, 149 mm.; August, 189 mm.; September, 27 mm.; and October, 1 mm.

Owing to the flat ground on which the town is built, drainage is a difficult matter, and with the increased rainfall it was not found possible to deal with all the flooding before mosquitoes had bred out in various places.

As a result, during the autumn of 1922 a severe epidemic of malaria occurred, affecting all classes of the population.

Additional factors which helped in the outbreak were:

a. The increased railway communication with the Southern Provinces, resulting in an increase of malaria carriers in Khartoum.

b. The presence of a British Battalion recently arrived from India, many of whom had previously suffered from malaria.

c. The presence of a crop of millet just outside the precincts of the town which bred mosquitoes *(Anopheles p. costalis)* owing to the heavy rainfall, and from which a large number of the civil population became infected.

The cases treated represented soldiers of the Egyptian Army admitted to the Khartoum Military Hospital.

The following table shows the total number of admissions:—

Month	Total admission	Total admissions of cases which contracted malaria in Khartoum	Total admissions of cases which contracted malaria out of Khartoum
August	7	7	—
September	316	297	19
October	533	497	36
November	243	232	11
December	215	198	17
Totals	1,314	1,231	83

The type of malaria.

The 1,231 cases of malaria who contracted the disease in Khartoum were divided into the following types:—

Benign tertian	421
Subtertian	709
Quartan	6
Undiagnosed	95
Total	1,231

The quartan cases were diagnosed clinically only, and too much stress cannot therefore be laid on them. Quartan malaria is uncommon in the Sudan.

Table of cases.

Primary cases numbered	864
Relapse cases	367 or 42.5 per cent.

The admissions for primary cases and relapses by months were:—

Month	Primary cases	Relapse cases
August	7	—
September	286	11
October	412	85
November	101	131
December	58	140
Totals	864	367

Table of relapses.

One relapse	158 or 18.4 per cent.
Two relapses	47 ,, 8.9 ,,
Three ,,	24 ,, 2.7 ,,
Four ,,	7 ,, 0.8 ,,
Five ,,	3 ,, 0.3 ,,

The large percentage of relapses is put down to the insufficiency of after-treatment. This will be discussed later.

The relapse cases were diagnosed by blood film examination, but in cases where this was negative by the periodicity of the fever, splenic enlargement and the interval since the previous attack, &c.

It was noted that the percentage of relapses amongst the subtertian cases was almost as high as those amongst the benign tertian cases. This is of course an unusual feature. There were but few cases of concomitant disease; in one case with five relapses the patient had just suffered previously from amœbic dysentery; and one with three relapses had active bilharzia.

The spleen incidence was as follows:—

(a) Benign tertian	....	44.6 per cent.
(b) Subtertian	....	47.5 ,,
(c) Quartan	....	45 ,,
(d) Undiagnosed	....	31.6 ,,

The average number of days in hospital for treatment was 6.3 days.

The average number of intravenous injections given "*before the temperature*" dropped to normal was 2.5, and the average total amount of quinine administered to each case intravenously and by mouth during the stay in hospital was $187^1/_2$ gr.

Treatment.

A purge of calomel or similar pill was first given, followed by a saline aperient daily.

The routine adopted in the treatment of all cases was by the intravenous injection of quinine.

A 1 c.c. or 2 c.c. syringe was used. The bihydrochloride of quinine in sealed ampoules of 1 c.c. containing 9 gr. or 6 gr., or a fresh sterilized solution of the bihydrochloride was employed.

Technique.

The arm was prepared in the usual way, and the upper arm compressed by a piece of rubber tubing. The contents of the 1 c.c. ampoule was sucked up in the syringe and an injection made into the median basilic or neighbouring vein. The quinine was injected slowly and steadily, the total time of the injection varying from 30 to 45 seconds.

Routine.

The normal routine adopted was as follows: Each patient was given one intravenous injection of 9 gr. of quinine bihydrochloride daily, until the temperature fell to normal. During this time he also received 20 gr. quinine bisulphate solution by the mouth, in two doses of 10 gr. each.

After the temperature fell to normal the intravenous injections were stopped, and 30 gr. of quinine bisulphate solution in three doses of 10 gr. each were given by the mouth until the patient was discharged.

After discharge, the patient attended the hospital daily, and received 10 gr. quinine bisulphate solution by the mouth for one month.

This routine was at times varied according to circumstances. If the temperature remained high, a second intravenous injection of 9 gr. would be given after an interval of six hours; in such cases only one dose of quinine was given by the mouth. At times, if the temperature was very high and the patient severely ill, two ampoules or 18 gr. would be given intravenously at once, followed by one dose of quinine by the mouth later in the day.

We have not given more than 18 gr. of the bihydrochloride by the intravenous route within a period of 24 hours, although at times as mentioned above this amount might be given at one time.

Effects of injection.

A total of 2,584 injections were given.

The injection was followed almost at once by an acceleration of the pulse rate, which varied from 5 to 17 beats a minute. Within a period of three minutes the acceleration had passed off.

Patients complained of a tingling sensation, especially in the mouth, ringing in the ears, and at times a feeling of constriction in the chest accompanied by one or two coughs. This rapidly passed off.

In one or two cases vomiting occurred, and in two cases collapse, with vomiting, sweating, rapid respiration and pulse, and dizziness. These symptoms passed off within a few minutes.

No cases of hæmoglobinuria occurred. All relapse cases were treated by further intravenous injections of quinine.

The records of three relapse cases are given below:

1. *Case A.*—Subtertian. Had six admissions during a period of three and a half months. Temperatures on admission were 104.8°, 103°, 103.4°, 105°, and 103° F. This case had a total of twenty intravenous injections and finally one injection of 606. Total period in hospital, fifty-two days.

2. *Case B.*—Benign tertian. Had six admissions during a period of three months, with ten intravenous injections. Total period in hospital, thirty-six days.

3. *Case C.*—Benign tertian. Had three admissions. Fifteen days previously had amœbic dysentery. Total of fifteen intravenous injections.

Those cases with four admissions received an average of 8.3 injections.

Those cases with three admissions received an average of 6.2 injections.

Those with two admissions an average of 4.3 injections.

Clinical observations.

The general type of fever throughout the outbreak was severe, and the majority of cases had to be conveyed to hospital as stretcher cases. There were 74 cases admitted with a temperature of 105° F. and 24 cases with a temperature between 105° and 106° F. inclusive. These cases of high fever were equally divided between the B. T. and subtertian types. There was only one case of cerebral malaria with unconsciousness, and there was no death recorded amongst the 1.314 cases.

After-treatment.

The relapses totalled 367, or 42.5 per cent. As stated previously, this large percentage was due chiefly, I think, to insufficiency of the after-treatment. Each case was ordered to receive 10 gr. of quinine bisulphate daily for one month, but in many instances the order was not efficiently carried out. The patients came from many scattered units in Khartoum, and for different reasons great difficulty was experienced in getting proper attendances. The men themselves had an aversion to taking quinine, and would get out of it whenever possible.

Neither would one expect that 10 gr. for one month would be sufficient to prevent relapses in all cases, but the cost of quinine in large outbreaks of this kind has to be considered.

Prophylactic quinine was administered to all troops in Khartoum from the middle of September onwards, in doses of 10 gr. weekly on two successive days. The efficacy of this treatment in reducing the cases of malaria was difficult to judge, and beyond having a favourable impression of this method of prophylaxis we are not prepared to make any definite statement.

It was of course instrumental in making the microscopic diagnosis difficult in many instances, and the 95 undiagnosed cases were due to this.

The adventages of intravenous injection.

a. The technique is simple, and can be effectively carried out in any hospital.

b. It is rapid, and one medical officer single-handed can treat a large number of cases.

c. The powerful effect of the drug is applied in a minimum of time and a maximum of effect.

d. It is less barbarous than intramuscular injection, there is a greater rapidity of effect, the absence of pain and any after-effects such as abscess or sloughing. The patients on discharge are not incapacitated by the results following on several injections into the buttocks.

e. By this method we claim that the period in hospital is shortened (the average stay was 6.3 days), always a consideration from an Army point of view, and in an epidemic when there is likely to be overcrowding of cases, accommodation is more rapidly set free, and the patients are fit for duty in a shorter time, thereby increasing the efficiency of the troops.

We recognize that the above notes are very incomplete, but observations are being continued.

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RADIOACTIVITY OF QUININE, ITS ANTI-MALARIAL MECHANISM

(RADIOACTIVIDAD DE LA QUININA, SU MECANISMO ANTIPALÚDICO)

RAFAEL COMENGE GERPE, MADRID

I.

In full empyricism.

THE mysterious energy which quinine diffuses in the organism has, up to now, remained completely unknown.

It may almost be said that all that is known was already known to the Indian Redskins, namely: that the said drug cures malaria.

A great deal of time has passed however since a noble Spanish lady made known in Europe the curative action of the pulverised bark of this tree, of the family of the *rubiaceae,* which *Linnaeus* himself studied and dedicated to the Spanish lady, creating in her honour the genus *Cinchona* (1632-39).

To-day it is said that quinine is a protoplasmic poison and with this, apparently true, affirmation, the troublesome question is considered to be settled.

There are however many protoplasmic poisons which will not cure malaria.

Protoplasmic poisons are, the aromatic acids and many of their derivatives *(Marfori);* tannin is a local one and also the salicylic acid about which *Pio Marfori* writes (1913):

> The most important property of salicylic acid is its action on the protoplasms; in extremely dilute solutions (1:4,000) it prevents diapedesis in the mesentery of the frog and in 1 per cent. it discolours the red blood corpuscles *(Binz).* Salicylate of soda likewise possesses, though in a lesser degree, the same action; thus, 1 per cent. solutions enfeeble the activity of the protoplasm of the lymphoid cells and the paramecia; vegetable protoplasm is less sensitive under the influence of sodium salicylate in respect of the active oxygen (resin of guayacum).

The antiseptic action of salicylic acid is noteworthy *(Kolbe and Buchholtz);* a solution of 1 per 1,000 of salicylic acid has the same antiseptic value as a solution of phenol of 1:850. Diluted to 1 per 1,000 salicylic acid prevents the development of fungi in wine, milk,

etc.; in 1 : 1,500 it prevents the development of the baccilli of carbuncle, in 2 per 1,000 it prevents the putrefaction of urine *(B. Celli)*. Salicylate of soda in 4 per 1,000 stops the development of bacteria in culture liquids.

On the enzymes likewise, salicylic acid shows itself powerfully active, as it prevents the action of the emulsine on amygdaline, of sucronine on sinigrine, and of pepsin on the albuminoids.

Finally, salicylic acid is endowed with energetic local actions. In concentrated solutions it coagulates albumen and acts on the tissues as an irritant and caustic.

According to *Manquat, Pouchet* "outlines the general action of salicylic acid in a happy way when he says that this substance *reduces the activity of the living protoplasm* by diminishing its activity (avidity for oxygen) and weakens the processes of anabolism and catabolism."

This same outline of Pouchet can serve for quinine.

If, in the cure of malaria, quinine acted as a protoplasmic poison, of necessity salicylic acid should exercise a much more energetic action, because, to the properties of a protoplasmic poison it adds that of being a good disinfectant.

Quinine is a bad disinfectant.

Quinine when it acts direct is a bad disinfectant; *in vitro* it has an action of little energy on bacteria. There are required according to *Binz* (1867), concentrations of 2 per 1,000 to prevent putrefaction. On ferments its action is similar to that which it develops on bacteria. On the other hand, it is more energetic against the lower animals.

Amebeae. — Solution of quinine hydrochloride 1 : 50,000
Death within six hours.

Paramecia	1 : 10,000
Infusoria	1 : 2,000
Carbuncle bacilli	1 : 625

Experiments of Rosin.

Rosin, cited by Professor *Hernando* of Madrid, found that *plasmodium* can live ten hours in a solution of quinine of 1 : 5,000, while a solution of methylene blue paralyses them at 1 : 10,000, stopping almost instantaneously the ameboid movements of the parasites.

Nevertheless, quinine is much more effective than methylene blue in the treatment of malaria.

Therefore against the hematozoa of malaria, quinine *apparently* has a much more energetic action *in vivo* than *in vitro*. I say *apparently*, because experiments carried out subsequently by me prove that

quinine *in vitro*, placed under certain conditions which I shall explain below, is as active as or more so than *in vivo*.

To what then is this *apparent* difference due? What new factor intervenes in the organism to increase so considerably the lethal properties which quinine develops against the hematozoa?

Why does this *protoplasm poison* increase its selectivity against the plasmodium in the mysterious laboratories where live matter appears to order rather than to obey?

Without any doubt, the factor which intervenes, the force which destroys the parasites in the blood, is not a chemical factor; it is not in direct contact, because methylene blue is seen to act directly *in vitro* with more efficacy than quinine, yet in the living organism quite the contrary happens.

This is the more striking when we observe that quinine circulates through the organism without undergoing any change in its characteristic chemical composition, is eliminated through almost all the glands and principally through the kidney, and is found unaltered in large quantities in the urine.

Consequently, it is permissible to believe that on the absorption of quinine and its circulation through the organism the molecular structure of the said substance undergoes strong vibrations; the hydrations and dehydrations, polymerizations, etc., all the numerous and various powers of the organism would intervene forcibly, causing the atoms of quinine to enter into constant movement, into perpetual vibration, without, nevertheless, altering its chemico-atomic molecular composition.

What would happen then? What will happen is that a new force will come into operation: *radio-activity*.

Because the salts of quinine, and above all the sulphate, by virtue of certain forces which make its atoms vibrate, emit light and become radio-active. It is some time now since this was demonstrated experimentally.

Experiments of Gustave Le Bon.

The experiments which I shall cite below were carried out in order to enforce a theory of scientific philosophy as to the constitution of matter and their author gives them no application in the medical field.

The eminent French scientist, *Gustave Le Bon*, in his fine work entitled: *L'évolution de la matière* (p. 385 etc.) says as follows:

"Among the various reactions which I have indicated on other occasions as accompanied by radio-activity of matter, there is the hydration and dehydration of sulphate of quinine. This substance, as was known some time ago, becomes phosphorescent by

the action of heat, but what was entirely unknown is that when it has lost its phosphorescence after having been sufficiently heated, it becomes brightly luminous owing to cooling, and at the same time radio-active. After having sought for the cause of the last two phenomena, I found that they were due to a very slight hydration. The radioactivity is only manifested at the beginning of hydration and lasts only a few minutes. The phosphorescence, on the contrary, persists for a quarter of an hour.

The property of sulphate of quinine of becoming phosphorescent by cooling is completely contrary to what is observed in the various phosphorescent substances, which never give phosphorescence when cooling.

In order to carry out the experiments of phosphorescence by cooling and of radioactivity with sulphate of quinine, it is heated to 125° C. on a metal plate until the complete disappearance of all phosphorescence. On being removed from the plate on which it has been heated, the sulphate of quinine *once more becomes phosphorescent on cooling, and being afterwards placed on the dish of the electroscope* it gives off for three or four minutes an abundant discharge of effluvia, which causes the leaves of the instrument to approach each other (12° during the first minute and 4° during the second). The dose used in our experiments was about 2 grams of sulphate of quinine. *The discharge stops long before the disappearance of the phosphorescence. The two phenomena are consequently independent.* According to the measurements which *M. Duboire,* professor of Chemistry of the Faculty of Science of Grenoble, carried out very carefully, the absorption of less than 1 milligram of water vapour is sufficient to make 1 gram of dried sulphate of quinine phosphorescent and radio-active.

The foregoing operation can be repeated indefinitely. When the sulphate of quinine is hydrated it is only necessary to heat it anew. It becomes phosphorescent by the heat, goes out, then lights up afresh by cooling with hydration and becomes radioactive. As the hydration and dehydration are the causes of the phosphorescence of sulphate of quinine this phosphorescence can be obtained on hydrating and dehydrating by any means differing from heat. Let us insert sulphate of quinine in a wide necked bottle with a little phosphoric acid anhydride, and close the bottle. The phosphoric acid will at once possess itself of the water of the sulphate of quinine. It will then be sufficient to open the bottle and blow into it to see the sulphate of quinine become brightly phosphorescent. If the bottle is then closed, the quinine salt is once more dehydrated and the same operations can be repeated a great number of times; sulphate of cinchonine gives the same results as sulphate of quinine, but they are less intense".

These very interesting experiments were confirmed by *M. Duboire* and by *M. Klanc,* and were finally repeated and confirmed by me. Nevertheless I have not been able to find anything in treatises on therapeutics regarding this curious property of quinine of giving forth light and becoming radio-active in consequence of a slight hydration, and I know of no author who ventures to give a serious explanation of the mode of operation of the said drug.

Let us see whether, bearing in mind this most important property of quinine, of becoming radio-active by reason of slight hydration, it is possible to explain the mode of its action in the organism and to disclose what is the weapon which destroys the producing agent of *malaria.*

To those who think of the practical importance of this modest

work I must point out that it merely constitutes an endeavour to emerge from the crude empyricism in which we are submerged.

It is perfectly certain that *Manquat*, in his excellent "*Traité élémentaire de Thérapeutique*" which I have before me, says: "It is useless to discuss at any length the mode of action of quinine in malaria". But on the other hand it is not less certain that if his gifted colleague and compatriot *Cl. Bernard*, professor of the College of France, had thought the same thing we should not know anything about the action of curare and possibly we should be unaware of the physiological function of the nerve motor-plates. Nor yet, if other investigators had followed the opinion of *Manquat*, would atropin be used for making clear the lesions of the pneumogastric nerve and it would not have been possible to make use of clinical examination of these and other elements which have so much contributed to clinical development and progress.

II.

Quinine is an almost inexhaustible source of radio-activity.

As follows from the experiments cited it is possible, merely by dehydrating and hydrating the sulphate of quinine, constantly to obtain light and radio-activity. As the experiment can be repeated an infinite number of times it follows that with a limited quantity of quinine there can be obtained a practically inexhaustible quantity of radio-activity. The quinine is not exhausted however much the experiment be repeated.

Quinine likewise undergoes no chemical alteration owing to containing more or less water of crystallisation. The crystals of quinine seen by me under the microscope before and after the experiment show no appreciable variation. With chemical reagents the reaction is entirely identical. It is like the platinum wire which, without altering its chemical composition, acquires entirely new properties on the passage of the electric current. The experiments set out below are directed to the object of illustrating this view.

How the same cause can produce opposite effects.

When the quinine loses water, owing to heat, the dry air or the dehydrating agent, etc., it shines in the darkness with a greenish light; if then it is breathed on, *keeping it still on the fire, etc., its light goes out* in consequence of the absorption of water, but lights up again when the breath stops. This operation of putting out the phosphorescence due to desiccation of the quinine by breathing, may be repeated as many times as required.

On the other hand, if we wait until this first phosphorescence of dehydration is extinguished and after having taken the quinine away from the fire, the action of heat or the drying reagent, it is again breathed on, the phosphorescence *which was previously giving out, lights up again* owing to action of the moisture of the breath. It is the phosphorescence of hydration which coincides with the diffusion of radio-activity. Thus there is the extraordinary case of a light going out with one breath and lighting up again by another.

This phenomenon is characteristic of the sulphate of quinine. It is likewise presented, though with much less energy, by sulphate of cinchonine. This difference suffices to distinguish them.

In order to explain this fact it would by necessary to modify slightly the theory of matter and energy. It must be supposed that some new force is released and that this is due to the dissociation of the atoms of quinine, otherwise we should have to admit the absurdity that, with a limited quantity of matter, an indefinite quantity of energy is obtained.

The author now describes how the phosphorescence is a simple means of detecting quinine in a powder, and further some experiments which prove that quinine *without acting chemically* diminishes the sensibility for light of silver salts.

The action of quinine recalls that of the anti-oxidases.

From the foregoing experiment it is seen that quinine retards the oxidation of salts of silver by light in the same way as it retards the oxidation of tincture of guayacum by the protoplasm of the potato *(Binz)*, extinguishes the phosphorescence of the schizomycetes and prevents oxidation of the erythrocytes.

These last three experiments were explained by saying that quinine, as a *protoplasmic poison*, operated by reducing the vitality of the protoplasm, and consequently its capacity of oxidation. In this case likewise, the quinine acts by preventing oxidation, *but the protoplasm does not exist*, and consequently the quinine cannot have acted as a poison by reducing any vitality.

Consequently it must be inferred that quinine has not acted chemically but by virtue of a physico-chemical action. By this *true action of presence*, which recalls the action of the anti-oxidases, quinine would operate by delaying the oxidation of all the protoplasms, and in this way would reduce the vitality of the cells on which it acts, by producing true cellular asphyxia. Thus its action on the cells appears a little more clearly and its mechanism becomes evident to some extent, not as a poison, but as a physico-chemical agent, capable of reducing and even preventing oxidations generally.

If this were not the case it would not be possible to explain what is the action of a substance which passes through the organism exercising an undoubted curative action, accompanied by very varied alterations in physiological conditions, and which is afterwards eliminated without having undergone any noteworthy chemical alterations and in a quantity almost equal to that which entered.

Comparison between the action of radium and that of quinine.

Continuing in the view of considering quinine as a radio-active medicine or the source of physico-chemical energy I decided to investigate the analogies of action between radium, the model of this class of medicaments. and quinine, the object of the present modest study. The following is the result of the comparison.

RADIUM	QUININE
Destroys the cells, the nutritive mutations of which are most rapid; whose process of nuclear division is shortest; which are richest in protoplasm, and which are cytogenitically youngest.	It destroys the *plasmodium* and other protozoa, still leaving untouched the cells which, like the erythrocytes, are older. Quinine exerts very little influence on the semi-lunar forms which have little or no reproduction.
The neoplastic cells are the first to die under its action.	Quinine has been used in inoperable cancer *(Jaboulay* 1900-1908); *Morton* (1893) advised the interstitial injection of the cancer focus with quinine in the treatment of cancer by X rays.
The phagocytes delay their amiboid movements under large doses; they exaggerate them under small ones.	The same is the case with quinine.
On large doses the glycogenic function of the liver diminishes.	In large doses it prevents the glycogenic functions of the liver and in small ones it stimulates them.
The volume of the spleen is reduced.	The same.
Plants are more resistent than animals, the major part of the microbes resist its action well.	Quinine which easily kills protozoa is likewise less fatal to bacteria.
Locally it is caustic and irritant.	Quinine is likewise in both cases.
Untimely use or excessive doses reduce the resistence of sound tissue.	When wrongfully used it reduces the resistence of the red corpuscles (haemoglobinurea, hematurea) and all the tissues.
Radium is analgesic *(Darier)* and also thorium *(Fobeau de Cournelles).*	Quinine is likewise analgesic.

RADIUM	QUININE
It makes chemical ferments inactive *(V. B Henri & André Mayer).*	The same.
The radium salts most in use are: sulphate, chloride and bromide.	Those of quinine are: sulphate, hydrochloride and hydrobromide.
The radium salts are phosphorescent.	It has already been seen that sulphate of quinine is likewise phosphorescent.
They give off cathode rays ionising the air.	Sulphate of quinine also emits a large quantity of cathode rays and discharges the electroscope *(G. Le Bon).*
It impresses photographic plates with its emanations.	As follows from the foregoing experiments, the sulphate likewise impresses photographic plates with its own radiations.
It is a chemical disintegrator and opposes the reactions of synthesis in large doses, while in small ones it stimulates them.	Quinine in large doses *reduces the activity of the live protoplasm (Pouchet).* In small doses it has for many years been used as a tonic and stimulant.
It improves exophthalmic goitre.	Quinine also improves it.
Radio-activity and X rays have been used successfully in malarial splenomegalia.	Quinine reduces the size of the spleen and cures the same splenomegalia.

Pharmacodynamics of quinine.

Let us follow quinine in its progress through the organism.

On reaching the stomach it is dissolved in consequence of the gastric acids *(Manquat).* The carbonic acid of the intestinal contents must exercise a favourable action on this process *(Gaglio).* In point of fact the quinine which precipitates in consequence of the carbonate of sodium, is not precipitated if there is added a dilute solution of bicarbonate of sodium with free carbonic acid.

The bile produces in quinine solutions a precipitate of insoluble glycocholate of quinine which is decomposed by the carbonic acid and by the alkaline carbonates. In the intestine where these acids do not exist the quinine is hardly absorbed at all, that is why it is badly absorbed when administered by enema. Quinine also exercises a twofold action on the epithelium of the stomach and the intestines according to the dose. In small doses it stimulates their function producing an increase of the digestive juices, thus stimulating the appetite and increasing the digestive functions.

With large doses or badly administered doses it *tannifies* the mucous membranes of these organs and the alterations of the absorption studied by *Heidenhain* and subsequently by *O. Cohnheim* present themselves. From these experiments it is deduced that with the poisoned

mucosæ results are obtained similar to those produced in the dead animal: absorption drops to disappearance point even with crystalloids and the intestinal wall loses its power *of only allowing itself to be traversed in one special direction*. These experiments serve to prove that absorption has for its basis a living and organised substance which is alone capable of effecting it.

As *Cohnheim* found, that the solution of sugar introduced into the poisoned intestinal loop, causes a considerable quantity of chloride of sodium coming from the sanguineous and lymphatic plexuses, the same thing happens with quinine, that is to say, after the administration of large doses purging effects occur, because the intestine gets filled with sanguineous plasm in consequence of the tannification of the mucosa.

These mucous membranes, in which necrosis is produced by quinine, lose the property of not allowing themselves to be digested by the intestinal juices; they are attacked and corroded by them, hence the gastrointestinal pains and the vomiting, which constitute a defensive symptom by which the said organs relieve themselves of the juices attacking them; owing to this defensive mechanism there will occur in the intestine anti-peristaltic movements, able to cause the bile to appear in the vomit.

In this way an obstacle to the drug is created; poisoning of the mucosa, suspension of the absorption and defensive vomiting.

"This protective function has in particular for its basis that capacity of *physiological selection* which we have found in the intestinal epithelium, owing to which, while they absorb independently of the laws of osmosis certain non-diffusible substances they do not allow themselves to be traversed by others which are more diffusible" *(Luciani)*.

With therapeutic doses these symptoms do not usually occur and consequently the quinine is easily absorbed, being found in the feces *(Kerner)*. But it may be stated that large doses capable of altering the mucosæ are not only not absorbed but they, if anything, prevent the absorption of all other substances.

When once it has traversed the gastrointestinal epithelium, quinine makes its way towards the liver through the portal system.

E. Cavazzani, studying the glycogenic function of the liver, brings out the following facts, which he copied from *Luciani's* physiology.

"Methylene blue, which does not alter the saccharifying action of hemodiastasis, when injected into the circulation, fixes itself preferentially in the liver and in a suitable dose prevents asphyxial hyperglycema and greatly reduces the post mortem glycogenesis. Nevertheless methylene blue, as was already known by earlier studies and has been confirmed by *E. Cavazzani*, possesses a strong paralysing action on the protoplasms".

"Likewise *bisulphate of quinine* which is indifferent for the enzymes and poisonous for the protoplasms, acts like methylene blue on the hepatic glycogenesis".

The liver stores all classes of poisons which, arriving by the portal vein, are detained by the hepatic cells, which accumulate them in a cytoplasm, destroys them in part, in part sends them to the intestine through the medium of the bile, and in part finally dissipates them slowly through the hepatic veins, so that they are afterwards eliminated by the renal emunctary.

Experiments carried out by *Schiff* (1861) and *F. Lussana* (1864) proved that the fatal dose for narcotic poisons, nicotine, hyosciamine, is much less by hypodermic injection than when injected direct into the portal vein.

This power of the liver of destroying or reducing the toxic action of alkaloids does not occur in other organs. *(Luciani).*

Mineral poisons may, as is well known, be rendered harmless and accumulate in this gland, which fact *Orfila* was the first to point out. The compounds of lead, copper, arsenic, iron, etc. accumulate in the hepatic cell. The accumulation of iron in the liver is important, being a fact which *Lussana* connected with the hematogenic and haemoglobinogenic action of iron medicaments, which was confirmed. *Marfori* (1893), in the laboratory of *Schmiedeberg*, finding in the liver a combination of iron with albumen similar to globin, to which he gave the name of *ferretine.*

Heger (1873-77) effected the artificial circulation of the isolated liver with defribinised and nicotinised blood, observing that on passing to the liver the nicotinised blood lost its characteristic odour. By subsequent investigations he found that the liver absorbs and retains from 25 to 50 per cent. of the alkaloids which passed through it (strychnine, quinine, morphia and nicotine).

Roger (1886-87-89-92) proves that:

"The solution of *quinine salts*, morphia, atropin, curare, etc., injected into the intestinal vein of the rabbit, show a toxicity nearly one-half less than when injected into the peripheral veins".

The liver degenerated by poisoning with phosphorus or rendered cirrhotic by ligature of the choleduct is no longer able to exercise any effective action against poisons. The same happens to the liver of animals which, owing to the effect of poisoning, have lost their glycogene. In the fœtal development also the appearance of the protective action of the liver coincides with the accumulation of glycogene therein.

Thus we see that this anti-toxic action of the liver is directly depend-

ent on the integrity of its cells and necessitates the presence of glycogene.

The hepatic cell has a marked dehydrating action on the sugar absorbed by the intestine, conveyed to the liver, and transformed there *into glycogene by a process of dehydration and polymerisation. (Luciani).*

Schroedel & Salomon, availing themselves of artificial circulation through the liver and chemical analysis of the blood before and after circulating through the said organ, found that if carbonate of ammonia be added to the blood it is transformed into urea, after having passed through the liver. This transformation is due to a synthetic process produced by the hepatic cell, by which the carbonate of ammonium, *by losing water,* is converted into urea. On passing the blood through the kidneys or muscles this transformation does not occur.

Consequently we are justifed in assuming that quinine undergoes in the liver a process of dehydration and polymerisation similar to the foregoing. Perhaps the glycogene (glycose without water) contributes, by hydrating itself, to this dehydration of quinine. For the rest, this is not in the least necessary because the solutions of radio-active substances are always radio-active.

The quinine dehydrated in the liver would pass on to the blood where, on being rehydrated, it would become more powerfully radio-active.

This radio-activity of hydration or dissolution, the former proved experimentally, would be the power which destroys the parasite of malaria, preventing its germination.

This must be assumed, because otherwise one fails to understand how this quinine, having such varied and powerful influences on all the cells of the organism, emerges unaltered with the greater part of the secretions, bile, tears, saliva, milk, urine, etc. Only in this latter is it found in a quantity of a third or more of the total dose and it has lost *its power of crystallisation* (amorphous inactive quinine of *Guglieni,* dihydroxilquinine of *Kerner).*

Action of quinine on the elements of the blood.

From the liver the quinine passes slowly into the blood circulation and gradually impregnates the blood and tissues, producing the exciting effects in all the cells, of small doses, both as regards radio-activity and quinine.

Afterwards, towards the sixth hour *(Manquat)* the degree of concentration of the quinine would be at its maximum, and it is then its

action makes itself felt on the elements of the blood and the tissues, reducing their vitality. It is thus seen that during the first moments the leucocytes increase their amiboidal movements and afterwards fall back into immobility. *(Pouchet).*

In large doses (1 : 20,000) of the weight of the body, quinine (like radium) reduces the number of leucocytes by $^1/_4$ after a few hours *(Binz, Scharrenbroich).*

Binz demonstrated a paralysis of leucocytes in the mesentary of the frog by the action of quinine, but these experiments were followed by others of *Hayem, Bochefontaine, Dusseldorf,* from which these writers concluded that the movements of the phagocytes are not reduced, but that, on the other hand, they flee by reason of a phenomenon of negative chimio-taxis.

It will be seen that at the bottom of this apparent contradiction of facts there is only a question of doses.

Assuming the radio-active emanation, it is seen that applying the quinine to the mesentary of the frog, its energy is able to stop and paralyse the movements of the phagocytes if the latter undergo its close and intense action, while they might likewise be able to defend themselves by fleeing to the deep parts before undergoing the action of radio-activity.

Subsequently the paralysing action of large doses on the leucocytes was demonstrated experimentally by *Vincent* in his study (*Tétanos et quinine*), in which he proves that the subcutaneous injection of quinine, owing to the inhibitation of the phagocytes, promotes the generalisation of the spores of the bacillus of *Nicolaïer,* producing a rapidly mortal tetanus, which very much recalls the splanchnic tetanus of *Binot.*

According to *Breguet,* quinine increases the fibrine and reduces the red corpuscles.

Binz, Manassein, Rossbach, assume that it fixes itself closely in the hæmoglobin, thus reducing the oxidising power of the blood. The experiments of *Binz,* carried out with blood freshly extracted from the organism, prove that blood oxidises the tincture of guayacum on adding spirits of turpentine, which gives up oxygen and assumes a blue colour; this reaction does not occur in the presence of quinine. He likewise found that the quinine clearly reduced the formation of the acids which the air, with the red corpuscles, produces in the blood. (*Binz, Zuntz*).

My experiments with silver salts tend to prove that quinine retards the oxidation similarly to antioxidases, by reason of a physico-chemical, or rather physical action. From these experiments it follows that

quinine, in order to reduce the oxidation of the blood, does not need to combine intimately with hæmoglobin, as was assumed by *Binz* and the writers above mentioned.

The rapid elimination of quinine, which appears in the urine ten minutes after its administration (*Piorry, Lavallée*) constitutes another argument against this intimate fixture of quinine in hæmoglobin.

Action on the muscular cells.

On the muscular cells quinine acts in small doses, increasing their capacity of contraction; in large doses it annuls this contractility. Thus the heart is seen with small doses, slightly to increase its rhythm, to augment its energy and to raise the pressure.

With large doses, weakening follows on a period of acceleration, with loss of energy and fall of the blood pressure over a long period. If the dose is fatal the heart stops in diastole.

Thus it happened in a case of *Giacomini,* cited by *Manquat,* where death occurred after taking 12 grams; another case of *Vaille*, etc.; this has also been confirmed on animals by *Laborde* and *Breguet.*

Although toxic doses are paralysing to the heart *(Lewitzky*, 1869), this organ is the *last to die (Bochefontaine).* "Probably a direct action of quinine on the heart is in question; the increase of the number of beats does not appear to be due to a reduction of the tone of the vagus nerve, because the paralysis of the vagus is not observed until after very heavy doses of quinine and then the paralysis is neither complete nor constant" *(Gaglio).*

The muscular fibres of the vessels contract with small doses of quinine, which fact contributes, on increase of cardiac activity, to increasing the pressure. With large doses the said fibres are paralysed and the vessels expand, reducing the pressure.

This paralytic vasodilatation explains the haemorrhage which quinine is capable of producing in highly vascularised mucosae. For this reason it is used in small doses in obstetrics, while in large doses it produces dangerous haemorrhage, which may even occur in the internal ear. In the said organ, owing to this paralytic vasodilatation, by large doses of quinine there is engendered a greater secretion of endolymph which is capable of producing tinnitus and deafness because the increase of endolymphatic pressure deranges the physical conditions in which the *Reissner* and the tectorium membranes function, and the physiology of the semicircular ducts is also altered, producing quinine intoxication.

The muscles increase their working strain, as there is likewise a direct influence of the quinine on the contractile element which is

observed even in frogs treated with curare *(Fallo, Piccinini)*. The uterus also increases its contractions during labour, even independently of the influence of the centres, when the nerves are severed. The spleen enlarged by malaria and the normal spleen are reduced in size by quinine.

In the dog it is possible to observe the contraction of the spleen under the influence of quinine. It is not a question of an action which is exercised on the nervous centres, because the spleen remains contracted even after the section of the nerves distributed through it *(Morier, Landois)*, if the nerves are first cut, then by vasomotor paralysis the spleen increases in volume; but nevertheless the quinine continues to contract the said organ.

On the nervous cells it exercises an identical action of stimulation in small doses, while on the other hand, in large doses it destroys their energy, producing analgesia.

The cellular interchange is stimulated by the radio-activity of quinine in small doses and reduced in large doses.

Its antithermic action is likewise explained by the reduction of cellular activity and by its action on the malarial agent.

Action on the plasmodium.

Quinine has an injurious action on the young forms of the protozoon, particularly in the extra-globular phase of life which follows complete sporulation. Likewise in the initial forms which have already invaded the red corpuscles, quinine exercises its action, preventing their further development. But when the stage of segmentation begins, quinine, even in heavy doses, is not capable of preventing the multiplication of the *plasmodium. (Antolini, Golgi, Schaudinn).*

On the semi-lunar forms quinine exercises no manifest action. The semi-lunar form represents a sexual differentiation of the protozoon which in man is sterile or highly infertile.

It is clear that quinine behaves as regards the *Laveran* protozoon in exactly the same way as radium, destroying the cells, whose nutritive changes are most rapid, whose process of nuclear division is shortest, which are richest in protoplasm and which are cytogenetically youngest.

These results confirm and explain what had already been observed by clinicists, namely: that quinine given during the febrile period (sporulation) does not succeed in suppressing the attack and that, for that reason, it is given during apyrexy, the doses being repeated so that the major part of the quinine administered reaches the blood a few hours before the attack, that is, when the germinating power of

the protozoon is greatest. Quinine exercises an action on *plasmodium* equal to that of radium and X rays on the ovarian cells.

The same may be said of quinine in relation to the agent of malaria as was said by *Don Sebastián Recasens* of radium.

"*Biological action of radium.*—On radiations of radio-active substances traversing the tissues, the cells absorb these radiations in greater or lesser quantity, undergoing cellular modifications in relation to the quantity, not of the rays traversing them, but of the rays absorbed by them.

The first action which is manifested in cellular life is the reduction of the genetic power of the cells. There occurs, not so much an alteration of composition, as an alteration of the vital function. On the cells radio-active substances always produce, similarly to X rays, a leucocitosis at the beginning of their action, with abundance of polynuclears. On maintenance of the radio-active action however a very pronounced leucopenia appears".

The red corpuscle which lacks germinating properties does not, for this reason, undergo the action of quinine.

Nevertheless, *Tomaselli* has described the icterohæmoglobinuric fever produced by large doses of quinine in which fever, hæmoglobinurea and icterus are associated.

Experiments with infusoria.

As a proof of what is said above I wished to determine whether dehydrated quinine is, at the moment of emanation of radio-activity, more fatal to infusoria than ordinary quinine.

With this object I carried out experiments in the Materia Medica laboratory, directed by the eminent Professor *Ivo Novi*, Professor of Therapeutics in the University of Bologna.

The infusoria of hay (paramecium aurelia) examined with slight magnification in a pendant drop, only die under the action of ordinary sulphate of quinine after a period which varies between five and fifteen minutes.

Quinine in powder was added to the drop, thereby forming a saturated solution. At the beginning of the experiment the infusoria were seen to swim between the crystals of sulphate of quinine and impelled by positive tactism, placed themselves against the crystals as if they were attracted, their movements were stimulated and finally they grew feebler and ended by turning round and round and dying.

With the same sulphate of quinine dehydrated in the heat of a gas burner, there is obtained the almost instantaneous death of the infusoria. They take at most from one-half to one minute to die.

Dehydrated quinine on contact with water becomes amorphous and assumes a yellow colour. This detail is interesting because at times the small quantity deposited in the drop is rapidly hydrated in contact with the moist surrounding air and then the infusoria do not die until the expiry of five to fifteen minutes, just as is the case with ordinary sulphate of quinine.

The influence of the heat does not operate, because when a fine tip of incandescent crystal is immersed in the drop the infusoria do not die.

I express my gratitude to the learned Professor *Ivo Novi* and to his assistant, Professor *Piccinini*, both for their hospitality and for the welcome they gave to this modest work.

To their advice and their most intelligent direction I am indebted for having carried out this study.

Conclusions.

1. Quinine must be considered as a radio-active medicament.
2. By virtue of this radio-activity it, in small doses, stimulates cellular vitality, but on the other hand produces the death of the cell in large doses, in a similar way to radium, first destroying their germinating power.
3. In this way we are able to understand its action on *plasmodium*, on diapedesis, etc.
4. Dehydrated and radio-active quinine is much more active on infusoria than non dehydrated quinine.
5. That it will be desirable to give proper study to the behaviour of quinine associated with radium and X rays in the treatment of cancer, malaria, etc.

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THE TREATMENT OF MALARIAL ANEMIA
(LE TRAITEMENT DE L'ANÉMIE PALUDÉENNE)

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IN *adults*, the best treatment for malarial anemia is *the systematic injection of quinine* every day, or every other day, when the attacks are recent; every third or fourth day when there has not been any attack for some time. The formula used in the army during the War, and given to a great number of soldiers on the Salonica Front, is excellent.

Bi-hydrochloride of quinine	0.80 gram
Urethane	0.40 „
Distilled water	2 c.c.

The injections must be given intramuscularly, with every strict aseptic precaution, in the gluteal region, with a long needle, and always above a horizontal line passing through the upper part of the gluteal furrow. Under this line there might be injury to the sciatic nerve, and yet it is in this region mostly that injections are made when given by persons other than doctors (nurses).

The patient is a different man after the third or fourth injection. The attacks have not recurred, the anemia has considerably decreased, and it completely disappears at the end of the treatment (12 intramuscular injections).

The treatment to be followed in severe malarial anemias will consist for the first year of two or three series of twelve injections of quinine, and of one or two series in the second year. This will be the best prophylactic treatment for malarial anemia, and the most favourable technique to master the resistent forms of the parasite.

Naturally, as regards the particularly severe forms, it will be a good thing to associate with the above the symptomatic treatment of anemia: Iron preparations (protoxalate in the dose of 0.15 gram morning and evening), hemopoietic serum in its various forms per os; preparations of cinchona bark, etc.

The *new arsenical compounds* were only exceptionally used before

the war, and systematically during and after the Salonica expedition. *Roques* in his inaugural thesis at Toulouse (1911), comes to the conclusion that atoxyl has absolutely no action. Hectine, on the contrary, gives remarkable results with the dose of 0.10 to 0.20 gram every two or three days, the series being of about 10 injections.

Arsenobenzol, Novarsenobenzol, Sulfarsenol, also give excellent results in malarial anemia. According to *Carnot*, it is the outstanding remedy. Give 0.10 gram at the beginning and increase by 0.15 gram at every injection: the maximum dose being 0.50 to 0.60 gram one injection every week.

Subcutaneous injections are sometimes painful; they seem to be less active than the intravenous injections. These must be preferred without any hesitation, but on condition that the anemia is not too accentuated, and also that the renal permeability is good. The determination of the *Ambard* constant is indicated before beginning such a treatment, as experience has shown that the renal complications need to be taken into consideration in malarial patients.

In 1917 we experimented with all the methods of treatment of malaria. Quinine given intramuscularly is a more powerful parasiticide than novarsenobenzol. However, the association of this medicament with quinine has a particularly good action on the blood as it increases the cell count and the hemoglobin rate. Besides this some subjects who have attacks now and then, in spite of good quinine treatment, doubtlessly greatly benefit from the association of arsenic and quinine. Recently, in a patient who had contracted malaria in Brazil, these two medicaments enabled us to obtain an excellent result where quinine alone had been clearly inadequate.

One injection of quinine (0.80) every week, and four days later an intravenous of 914 (0.15, 0.30, 0.45) net exceeding this dose (10 injections of quinine and about 3 grams of 914). Fowler's solution, sodium cacodylate, arrhenal, have also an undeniable action on the general condition and on the blood, in malarial anemia.

A certain amount of data concerning the good effects of splenectomy in malarial cachexia, and anemia with splenomegalia, was published previous to 1914.

According to *Sabadini* of Algiers, and *Bouguet* of Beja, every patient with malaria and an enlarged spleen, with cachexia, and severe functional troubles, must be operated on. It is certain that when this intervention is successful it determines the disappearance of abdominal pains, improves the general condition, ameliorates the anemia, and does away with such dangerous complications as rupture of the spleen, torsion of the pedicle, abcesses, infarction.

The objection may be raised that despite the splenectomy, malaria is not cured, that the operation is a severe one, as it has a mortality of 25% according to *Kopylon's* statistics on 200 cases. The possibility of such an operation will therefore only be considered after complete failure of the medical treatment. Splenectomy gives a higher death rate than exosplenorexy *(Vincent's* operation), the effects of which are less rapid, but which has the advantage of avoiding any serious risks to the patient. Besides, in the case of irreducible malarial splenomegalia, it would be good before attempting the extirpation of the spleen, to use *radium* applications as *Quénu* and *Degrais* did successfully in 1923.

In *infants* the best way to stop the progress of deglobulisation and enable the rectification of blood disturbances, is to make intramuscular injections of 5 ctgr. of quinine formiate every day, and later every other day. A series of 8 to 10 injections is generally enough to stop all rise of temperature and to show an improvement of the anemia, without having to use at the same time the iron medication. It will however be preferable later on to give some iron protoxalate (0.20 gram per day) for ten days, once or several times, so as to enable the organism to reconstitute its iron reserves which dwindle away so much the faster if the child has not been treated from the beginning of the illness. If during the following month, even in the absence of any attack, the anemia has a tendency to reappear, or if the spleen increases in volume, a new series of 6 to 8 injections of quinine formiate will be given, one injection every third or fourth day.

Quinoforme Lacroix, because of its excellent preparation and its perfect conservation, will render real services to adults as well as to children.

A change of climate and especially the sojourn of malarial patients in a temperate climate like that of France is excellent at all ages. A *mineral spring* cure is the more indicated for malarial anemia because the hematopoietic organs, liver and kidney, are out of order.

The association of high altitude climate and arsenic treatment (la Bourboule) gave *Boudry* remarkable results. He noticed that after a month's treatment the hemoglobin rate increased from 7 or 10 to 11 or 12; but especially that the proliferation of red corpuscles is so intense that a return of the number to the normal is the usual thing.

Malarial anemics will very much benefit from a first cure at Vichy, followed by a stay in a climatic resort.

Lombart of Geneva, quoted by *Maurel*, thinks that a medium latitude (3300 ft.) is advisable for anemic conditions due to frequent

chills with large spleen, anorexia and the whole retinue of malarial cachexia. On the contrary, this author met with pernicious attacks at high altitudes in malarial subjects who had been sent there direct without a preliminary sojourn at lower altitudes. The malaria patient will therefore preferably be sent to the resorts of Auvergne, which are, in the order of their intensity of arsenical mineralisation.

La Bourboule with 5 mlgr. 6 of arsenic corresponding to 28 mlgr. of sodium arseniate and 32 drops of Fowler solution.

Vic-sur-Cère with 3 mlgr. arsenic.

St. Nectaire with 0.8 mlgr. arsenic.

Le Mont-Dore with 0.4 mlgr. arsenic.

(*Revue Pratique des Maladies des Pays Chauds et Egypte Médico-Chirurgicale*, Paris. **3**: N. 3, Nov. 1923, p. 190—210).

MALARIA DURING PREGNANCY TREATED WITH HEAVY DOSES OF QUININE

(PALUDISME AU COURS DE LA GROSSESSE TRAITÉ PAR DES DOSES MASSIVES DE QUININE)

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THE two cases given below show that the administration of quinine even given in a very large dose has no ill effect on the course of pregnancy in the early months.

Case I.

C . . ., 24 years of age, of French origin, has for two years been living on the West coast of Africa.

In March 1922 pregnancy begins, the first two months passing normally. In the third month miscarriage by two stages without any febrile condition resulting. The woman attributes her miscarriage to fatigue, but she remembers having had two or three attacks of fever during the two or three weeks prior to the miscarriage, her temperature having gone up to 39°-39·5° C. Since her arrival in the colony she has been taking 0·25 gram of quinine every day, which dose she never exceeded.

Examined on the 20th February 1922 at Dakar. Medium stoutness and stature. Well built, general condition good; no syphilitic sign.

There is a slight presystolic murmur due to mitral stenonis, but there is no sign of heart strain. Urine normal, spleen and liver normal.

She is found to be two months advanced in pregnancy, which is taking its normal course after a miscarriage, due perhaps to malaria. We advise 0·50 gram quinine every day instead of the usual 0·25 gram.

24th January 1924. Called to the patient urgently at 11 p.m. we find a typical attack of paludism with a temperature of 40·2° C. The patient complains of some pain in the abdomen and fears a miscarriage. No vaginal discharge. We supervise immediate administration of 2 grams of sulphate of quinine in 4 cachets of 0.50 gram each.

25th February. About 8 in the morning: one gram of sulphate of

quinine per os. Temperature 37·5° C. No abnormal uterine feature.

About five p.m.: once more one gram of sulphate of quinine. Temperature 37·8° C. No uterine contraction.

Therefore, within less than 24 hours 4 grams of sulphate of quinine were taken. The heart showed no weakening, there was no vomiting, but some diarrhoea and reduction of urine quantity. The clouding of the mental faculties due to quinine was pronounced for half a day: muscae volitantes, tinnitus aurium, and deafness, which soon disappeared.

26th February. No more fever. The elimination of urine satisfactory. One gram of sulphate of quinine internally morning and evening. Same treatment during the four following days.

In 7 days therefore the patient took 16 grams of sulphate of quinine internally, four of them during the first 24 hours.

The blood film taken at the time of the attack showed that the agent in question was the parasite of tropical fever, the *plasmodium praecox*. Some red globules contained two and three parasites.

From the 3rd March onwards: one gram of quinine in two portions per day.

We were able to follow the course of this pregnancy until the middle of April, when our patient, then four months advanced and in good health left for France.

Subsequently we learnt that this young woman, on her return to France, had a slight malarial attack, but had given birth in due course without any complications, to a boy, alive, of good physique and developing normally.

Case II.

R . . ., A Frenchwoman of 23 years of age, arrived in Senegal in August 1912 for her first stay in the colonies. During the first few weeks no hygienic precautions, neither mosquito net nor quinine. At the end of September 1923, feeling unwell and feverish for a week, headache, contracture, very pronounced lassitude. Following the advice of several people she takes 0.25 gram of quinine per day.

Early in October 1923, feverish attack, temperature rises to 40.2°. C; one gram of quinine prescribed.

On the 6th October I am called in the morning — a new attack of fever having occurred. I find a woman of strong physique and good figure who has never had any previous illness. No sign of syphilis. The malarial attack is typical, the temperature is 41.2°. C.

The patient is pregnant for the first time, the pregnancy being four months old. Heart sounds not yet audible. For some hours past has

had pains in the lower abdomen, corresponding to the uterine zone and kidneys. No vaginal discharge. Urine contains no albumen; all organs normal.

We advise quinine administered intramuscularly, but the patient refuses, having heard of the abscesses which sometimes follow injections of quinine. We then prescribe complete rest, enema containing laudanum, and 2 grams of hydrochlorate of quinine to be taken in cachets of 0.25 gram each every two hours.

7th October. Feverish night, vomiting once. At 9 a.m. 39.3°. C. pains in abdomen continue, without vaginal discharge.

We strongly insist in favour of a more energetic treatment especially as, from a blood film taken the day before, we find the existence of numerous hematozoa, of the form of *plasmodium praecox*. The patient agrees to injections of quinine and receives in the course of the day:

At 9 a.m. 1 gram of hydrochlorate of quinine intramuscularly.

At 2 p.m. 1 gram of hydrochlorate of quinine internally in 4 cachets.

At 6 p.m. 1 gram of hydrochlorate of quinine intramuscularly.

In 48 hours this young woman, about four months advanced in pregnancy, has therefore received 5 grams of quinine, two grams by intramuscular injection and three grams internally.

8th October, a better night, temperature 37·5°. C. Common signs of cinchonism: tinnitus, muscae volitantes and slight redness on chest. Abdominal pains have stopped. During the day 2 grams of hydrochlorate of quinine in 8 cachets.

9th October. Temperature 38°. C. Two grams of hydrochlorate of quinine intramuscularly at 10 a.m. and 6 p.m.

10th October. Temperature 37·3° C., one gram of hydrochlorate of quinine in 4 cachets.

11th October. Temperature 36·8° C., same treatment.

12th October. Temperature 36·7° C., 2 grams of hydrochlorate of quinine in two intramuscular injections.

From the 6th October to the 12th October, this woman has absorbed 13 grams of quinine, namely 6 grams by intramuscular injection and 7 grams internally. The few hypogastric pains which might first have caused an apprehension of miscarriage disappeared; no anxiety exists in that respect.

From the 13th to the 16th October 1 gram of hydrochlorate of quinine per day in 4 cachets.

From the 17th to the 23rd October 2 grams of quinine per day in 8 cachets of 0·25 gram at intervals of two hours.

On the 18th October an examination of the blood shows the total

absence of hematozoa, there are no more pigmental granulations in the mononuclear leucocytes.

From 23rd October to 23rd November 1 gram of quinine per day.

Towards the end of October active movements and heart sounds of foetus perceptible.

We advise the patient to take every day from the 23rd November to the 23rd December 0·75 gram of hydrochlorate of quinine in 3 cachets and after that, every day, as long as she continues to live in Senegal, 0·50 gram of hydrochlorate of quinine in 2 cachets.

Summary.

These two cases relate to two young women, one two months and the other four months advanced in pregnancy, attacked with paludism and threatened with miscarriage, and who, on being treated with quinine in very large doses, did not miscarry, the pregnancy running its normal course and the children being born alive and well. They absorbed, both internally and by intramuscular injections, 16 grams of quinine in 7 days and 31 grams of quinine in 17 days respectively. These two facts speak in favour of the harmlessness of quinine during pregnancy. They even suggest that the fact that a miscarriage was prevented is due to this intensive treatment.

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A CASE OF CONGENITAL MALARIA

(UN CAS DE PALUDISME CONGÉNITAL)

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THE case may be summed up as being that of a woman who, on the occasion of an acute period of malaria, prematurely showed the beginning of labour pains. The pains were stopped by the action of quinine on the malarial attack. Some time later the patient has a new attack during which she gives birth to a live child, the blood of which as well the blood of the chord, contained hematozoa.

Dolores E., a Spanish woman, 25 years of age, arrived in Senegal in 1918. Shortly afterwards contracted malaria. Since that time very irregular malaria attacks, about which the patient never troubled. Other pathological antecedents of insignificant value. No signs of syphilis.

In 1919, first pregnancy: normal confinement at the right time, with well formed girl, who dies five months later from some undetermined ailment.

In 1921, miscarriage at 5½ months with normal sequelae.

In 1922, fresh pregnancy. Enters native Maternity Hospital at Dakar on 15th December. Pregnant about 7½ months, cephalic presentation; heart sounds good. To the touch uterine neck very soft, about 3 centimetres long, closed. Pelvis normal.

Well built woman, but run down and feverish. T. 38° C., P. = 82. Headache. Physical examination of organs disclosed nothing special. Urine slightly albuminous.

Treatment: rest, milk diet and purgatives, 0.25 gram of quinine every day.

16th December, same condition. T. 38° C., P. 86. There has been vomiting of food and patient complains of abdominal pains.

17th December. T. 39° C., P. 100. Bilious vomiting, constipation, abdominal pains.

Examination of the blood shows the presence of numerous hematozoa having the form of *plasmodium praecox*. The urine is purulent and contains very numerous cocci. During the evening, irregular abdominal pains of intermittent character and accompanied by uterine contractions. Patient transferred to labour ward.

Shortly afterwards, malarial attack. T. 40.8° C. with shivering for 1½ hours, then heat and sweating. As soon as the shivering starts, the patient is given, by intramuscular injection, 1 gram of hydrochlorate of quinine. Two hours later a further intramuscular injection of 1 gram of hydrochlorate of quinine.

During the night the uterine contractions are at great intervals. About 3 o'clock in the morning the neck is incompletely effaced, the dilatation the size of a florin piece, the amnion swells on each contraction; heart sounds are good.

On the 18th December uterine contractions cease at 5 in the morning; about 7 o'clock repeated bilious vomiting. Temparature 38° C. The patient is very prostrated, no longer answers questions, swallows liquids with difficulty. Urine rare, dark in colour; bilious fever with hemoglobinurea is feared, but there is no icterus.

Two injections of bihydrochlorate of quinine are then made intramuscularly of 1 gram each. In the course of the day relaxation of the general phenomena; the patient is made to take abundant liquid; vomiting did not recur.

19th December, general improvement. T. 37.5° C. Urine clearer, 1.200 litres, albuminous, contains a little pus.

No abdominal pain, no uterine contraction. Length of neck about 2 cm; can be traversed by a pencil; heart sounds good. Prescribed: water and milk; urotropine 1 gram; hydrochlorate of quinine 2 grams in 4 cachets of 0.50 gram at intervals of 4 hours.

On the 20th, 21st and 22nd December, general progressive improvement. Same treatment: urotropine, 2 grams of hydrochlorate of quinine in 4 cachets.

23rd December, at her express request this woman leaves the Maternity Hospital to go home. Pregnancy takes its normal course; no pain, no contraction, foetal heart sounds good.

From the 17th to the 22nd December, that is, 6 days, this patient therefore absorbed *12 grams of quinine hydrochloride, 4 of them by intramuscular injection*. At the same time the onset of labour was stopped and the severe malarial attack from which she was suffering was forced under.

Unfortunately, after leaving the Hospital, the woman did not continue any treatment and she was again seized with pains and

malarial troubles, so that it was impossible to stop premature labour.

On the 4th January 1923, she therefore came back to the Maternity Hospital, suffering once more in the abdomen. Slight uterine contractions are found. Foetal heart sounds good. General condition satisfactory. T. 37.1° C., P. 75. Given: urotropine and then quinine, 1 gram in 2 cachets. In the night uterine contractions gain in intensity. At about 3 in the morning the woman is transferred to the labour ward. Foetal heart sounds are good; dilatation about the size of a four shilling piece.

Malarial attack starts almost immediately with shivering for one hour. An intramuscular injection of 1 gram of quinine hydrochloride was made at once.

During the heat stage of the malarial attack, at 4.30 a.m. the patient gave birth to a living child, of the male sex, weighing 2,200 grams. Natural delivery, the placenta weighing 400 grams. On termination of delivery renewed intramuscular injection of 1 gram of hydrochlorate of quinine. Postdelivery period normal; 2 grams of quinine in cachets of 0.50 gram each. On the sixth day after the confinement the patient leaves the hospital.

The prematurely born child, of good physique, shows during the days following his birth, excessive cyanosis and coldness. On auscultation the heart is found perfectly normal. The child nevertheless showed a particularly intense icterus, which appeared on the day after his birth, and took its course without fever.

We have no further information either about the mother or the child after they left the Hospital.

In connection with this case we made some enquiries which enabled us to trace out here an example of congenital paludism, due to the transmission of the maternal hematozoon to the foetus through the medium of the placental circulation.

Doctor *Léger*, director of the Institute of Biology of French West Africa, was good enough to take our preparations and confirm our results, for which we are indebted to him. He was particularly qualified for this work as he has himself published a case of *Congenital paludism* (*Soc. Path. Exotiq.* vol. XI, No. 10, 1918).

The following were the enquiries made by us:

a. On the 17th December, when the woman first entered the Maternity Hospital, an examination of her blood showed the presence of numerous hematozoa: *plasmodium praecox* form.

b. On the 5th January we took blood films of the umbilical cord,

the child having been born during the full malarial fit of the mother, and we find therein schizontes of *plasmodium praecox*.

c. On the 7th January, a new film of maternal blood, in which, in spite of the intensive quinine treatment, hematozoa of the form *plasmodium praecox* are found, the protoplasm of which was irregular and strongly modified by the action of quinine.

d. On that same day, the 7th January, the second after the birth of the child, which already showed an intense icterus, we took some of its blood, an examination of which gave us the following particulars:

1. Numeration of corpuscles:
   - red corpuscles 5,130,000
   - white corpuscles 30,000
2. Formula of leucocytes:
   - polynuclear neutrophiles .. .. 71 %
   - „ eosinophiles .. .. 1 %
   - „ basophiles .. .. 0 %
   - mononuclears large .. .. 18 %
   - „ medium .. .. 7 %
   - lymphocytes .. .. 3 %
3. Parasites: in certain very strongly red corpuscles the presence of *schizontes of plasmodium praecox*, but rare.

Summary.

A woman in the eighth month of pregnancy a sufferer of long standing from paludism, presents premature onset of labour under the influence of a severe malarial attack. The labour was stopped on the patient being subjected to quinine in large doses (4 grams in 48 hours by intramuscular administration).

Nevertheless confinement takes place three weeks later, while a malarial attack is in full progress. The presence of hematozoa is detected in the blood of the umbilical cord, and again, two days after the birth, in the blood of the new born child, there is found the same variety of hematozoa, which had been detected in the mother and found in the blood of the umbilical cord.

It is therefore truly a case of intra-uterine transmission of the malarial infection of the mother to the foetus.

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NEW CONTRIBUTIONS TO THE KNOWLEDGE OF PARASITOLOGY, TROPICAL PATHOLOGY AND HYGIENE

(EINIGES NEUERE AUS DEM GEBIETE DER PARASITOLOGIE, TROPISCHEN PATHOLOGIE & HYGIENE)

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ON the treatment of malaria the author writes, inter alia as follows:

From the *therapeutic* point of view mention may be made here of the works of *Léger* and *Bédier* (1923) and of *Stradomsky*. *Léger* and *Bédier* also emphasize the effect of quinine on the intraglobular stage of the parasites, which the present writer himself has always insisted upon, in tertian malaria. Also according to *Stradomsky* (1923), there is not a single method of fighting malaria which gives an absolute certain result. The case material must be under careful observation for at least one year. Tertian patients who received in the autumn a series of intravenous quinine injections, showed, after 300 days, 82% relapses and only 18% free from relapse, whereas after *one* month only 12% had relapsed. The administration of the quinine per os or intravenously and also the combination thereof, led to equal results. The combination of quinine with neo-salvarsan was likewise no safeguard against relapse. Methylene blue exhibited the same results in combination with quinine as pure quinine treatment(!). Intravenous injections were indicated in coma, severe vomiting and disturbances of the digestive tract. Intravenous injections act more speedily in arresting an attack and require a minor quantity of quinine. It is not the quantity of quinine which is decisive as regards the final outcome, but the duration of the treatment.

In tertian, which starts in spring and summer, treatment should be continued until the arrival of cold weather and then interrupted until the period of relapse, then again continued for 2 to 3 months. In tropical malaria the treatment should last 3 or 4 months. It should be desirable to give the quinine one day before and on the actual day of expected relapse. Injections of adrenaline were not found capable of provoking an attack, but are said materially to assist the detection of the parasites in the blood, particularly the tropical gametes. The writer, a short time ago, uttered a warning against adrenaline injections owing to possible severe consequences.

(*Medizinische Klinik*, Berlin, **20:** No. 47, 23 November 1924, p. 1662)

THE EFFECT OF MALARIA ON THE NERVOUS SYSTEM WITH SPECIAL REFERENCE TO THE MALARIAL PSYCHOSIS

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THE author concludes his article with the following summary and conclusions. That there is a malarial psychosis can be definitely stated, but on account of many factors, its physiognomy is of necessity varied.

Of the determinants giving a diverse mental picture may be mentioned: Alcohol, severity of the attack *per se*, age of the patient at the onset of the malarial attack, even the acuteness or chronicity of the disease, and lastly, hereditary taint. A few manifestations however, are quite constant, such as initial mental confusion, oniric delirium and more or less complete delirium.

The symptoms of a malarial intoxication with its oniric delirium resemble those of other toxic infectious psychoses. They are modified somewhat by hepatorenal insufficiency.

Although patients with a material psychosis are frequently found to have been alcoholic at the time of onset of the disease, and although malarial patients are capable of easy alcoholization, alcoholism has not been found to be a necessary accompaniment.

Arabs, who were not as a class alcoholic, whenever they developed a malarial psychosis, lacked the initial delirium, while Europeans with an alcoholic taint, on the contrary, always developed an initial delirium. This is so constant that several observers have taken it as an indication of alcoholism.

The severity of the malarial attack in a susceptible individual is on a quantitative basis, and so determines his reaction. With a florid attack the quantity of malarial toxin is greatly in excess of that of a mild attack, so that in the former case we would expect greater mental aberrations than in the latter.

Depression has been most frequently observed in children.

Jews as a race tend to develop a catatonic reaction.

The mental symptoms appearing with the first infection of malaria are generally:

1. Delirium, which is intermittent, not very well sustained, rather monotonous and not expansive;
2. Confusion with dream delirium, followed by amnesia dating from the onset of delirium and varying in its completeness.

In chronic malaria the individual attacks are less severe, less noticeable, generally taking the nature of a depressed mental state, and gradually shading into a neurasthenic or hysteroneurotic condition.

A nervous system with hereditary taint is suitable soil for the development of a malarial psychosis. This and the malarial toxinfection are in themselves capable of setting up mental aberrations in a patient, but probably as often as not alcoholism is also present. This in turn aids the malarial intoxication and results in a mental upset.

Twelve cases of malaria in patients suffering from several different types of psychoses (non-organic) did not show added psychotic symptoms. The failure to elicit mental phenomena due to malarial intoxication, however, does not detract from the hereditary factor in malarial psychoses. Old hospital cases on "back wards", not subject to the careful scrutiny and study that newer and more hopeful cases demand, might easily develop some few new mental symptoms under a malarial attack and have these overlooked. Again, in non-organic cases already on a low mental level, living the well-protected life of an institution, malarial infection might conceivably be insufficient to bring out aberrant mental reactions, such reactions as might be termed significant of a higher mental state bearing the brunt of a toxic infection.

In one case herewith reported, paresis could not be definitely ruled out, although the tendency was to believe that his mental upset was due to malaria. In this connection it is interesting to note that *Pilcz*, using *von Wagner's* treatment for general paralysis, occasionally noticed acoustic hallucinations, ideas of persecution, delirious and catatonic states in those subjets infected with malaria. All their symptoms disappeared when quinin was given.

Pathologically, of outstanding importance is the plugging of small arterioles and capillaries in the brain and spinal cord. The thrombosis or embolism in perforating arterioles, if not fatal, causes the most serious consequences. This tendency to thrombosis and embolism partly explains the presence of almost any of the topographical neurological syndromes noted occasionally in the course of malaria. Most interesting, as well as most rare, is the development of motor aphasia, due to the blocking of capillaries surrounding *Broca's* area.

The delirium is well explained by the marked hyperemia of the

pia vessels, subarachnoid perivascular and pericellular spaces, and plugging leading to punctiform hemorrhages.

The development of coma is found to be due, aside from such preëxisting conditions as anemia, cachexia, physical or mental fatigue, the puerperium, insolation and alcoholism, to the number of parasites present, the amount of toxin secreted and, most of all, to localization of the toxi-infection in the brain.

In cerebral malaria the symptoms may simulate any brain disease, but the mental symptoms are not commensurate with the cerebral trauma due to the parasites *per se*. They are exaggerated, and point to a cerebral intoxication.

Neuritides, neuralgias, hyperalgesia, headaches, and acute hyperpyrexial attacks are but indications of the effect of malarial toxins on peripheral and central neurones.

Amnesia of malarial origin is conditioned by the lack of attention during and after the initial delirium, and is of varying grades. One case studied had an amnesia for six months.

As aforementioned there is a difference of opinion on the exact clinical picture exhibited in a malarial psychosis. From the first there is a bradypsychia which observers have found to progress to a frank depression. Maniacal outbreaks, not frequently observed, can only be attributed to a constitutional predisposition. Depression is always in varying degrees in those long affected with a malarial infection. One writer explained this from the fact that most of his cases of malarial psychosis were in women, and they are the more given to depression. Racially speaking, Jews, when affected with malaria, have been found prone to a catatonic development. Several observers have noted that the malarial mental confusion has, for its essential character, the accompaniment of certain symptoms which evolve toward dementia precox catatonia. In my first case of malarial psychosis it was the consensus of opinion that the patient was a case of catatonic dementia precox. Each consultant, however, expressed some doubt as to the diagnosis, and was wont to give malaria as the possible cause of the development of the psychosis.

Malaria over a period of years, with a history of rather frequent outbreaks, is capable of bringing on a marked neurasthenic condition. Aside from the possible psychic effect of a chronic debilitating infection, malaria attacks the hemopoietic function and vitiates it at its source, thus making the patient a fit subject for neurasthenia.

Epilepsy and hysteria, according to good observers, are caused by malaria, and in preëxisting conditions the infection serves to aggravate the symptoms of both.

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MALARIA AND THE ANTI-MALARIAL CAMPAIGN DURING RECENT YEARS

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It has been stated that malaria has probably killed more human beings than all the wars that have ever devastated the earth[1].

We do not speak of the elimination of malaria, but if one can get it from 50 per cent. down to 5 per cent. in a year or even to 2 per cent. or 0.5 per cent., one controls the disease, and that can be done[2].

HYGIENIC measures and quinine are the two extremes between which the question of anti-malarial measures oscillates. Both have their adherents who mostly expect a result by the one or the other method, while a third group tends more to a combination of both.

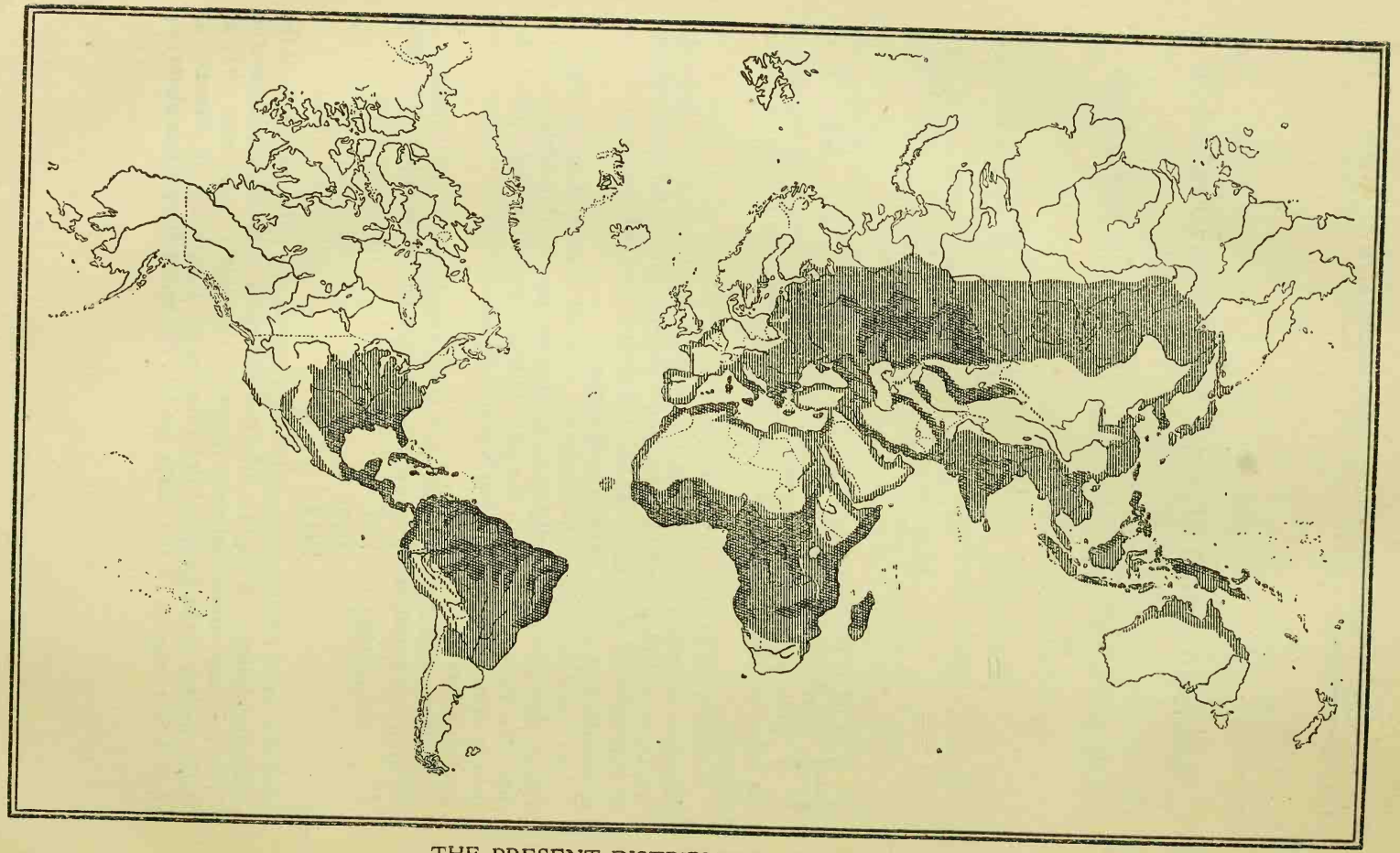
There is practically no divergence of opinion as to the extent and diffusion of malaria over the whole world, its influence upon the health of peoples, and its retarding effect on the social development of extensive areas. And it is said that malaria was an important factor in the decline of the ancient civilisation.

Increased systematic investigation, clinical as well as microscopical, shows that there is hardly any country in the world in which malaria does not occur, and when we give below some statistical figures, this is only done to illustrate what has already been known for a long time among experts.

Thus we find that in *Morocco*[3] the Committee of the Ministry of War gives the following data for the country of the Djebala and the Riff:

Morbidity in 1917	107.2 per 1000
.. .. 1918	79.6 .. 1000
.. .. 1919	297.7 .. 1000

and the year 1920 threatened to be even worse. Fifty per cent. of the effective military strength is infected with malaria in the first 12 months. The military investigation committee calculates that from 1917 of 1920 inclusive the hospital-days for malaria entailed an expense of 6,938,666 pesetas to the State, and *F. Blasquez Bores*[4] has observed,



THE PRESENT DISTRIBUTION OF MALARIA

that in the environs of Tétouan, his battalion of 890 men had in 1916 286 sufferers from malaria with 32 fatal cases; in 1917 680 sufferers with 54 cases and in 1918 in 850 men, 650 cases and 87 deaths, which means that the mortality was 14 per cent.

The general morbidity for malaria of the Spanish Army in 1917 and 1918 was:

Ceuta	in ..	23,491 men ..	5,944 cases
Melilla	„ ..	23,196 „ ..	2,605 „
Larache	„ ..	12,485 „ ..	2,525 „

which means an average morbidity of 93 per 1000 per annum.

In *Algeria*[5] at Hennaya in a selected school out of 326 boys and girls 60 had enlarged spleens.

In the *Saharan oases*[6] the splenic index varies from 12 per cent. (Tadmit) to 40 per cent (El Goléa).

In *Khartoum*[7] in the year under report (September 1921—October 1922) an epidemic of malaria, which comprised about 10,000 cases, occurred in the city of Khartoum and neighbourhood. Out of 1367 notified cases, 1071 were considered to be local infections.

In 210 children examined in *Dakar*[8] and Medina the parasitic index was:

	Dakar	Medina
in children under 10 years of age	43.7	63.6
„ „ over 10 „ „ „	30	59.6

After a preventive treatment with quinine from October 1922 till July 1923, the index was:

	Dakar	Medina
children under 10 years of age	23	22.7
„ over 10 „ „ „	22.2	21

In the same region[9] during December 1922—1923, 7.637 children from 15 days to 3 years were examined.

The average proportion showing acute clinic manifestations of malaria was 17.14 per cent. for the whole year; the highest proportions of children affected were during the rainy season June—November 1923.

At Kaolack (*S.W. Africa*) *Delbreil*[10] found that all children under 5 years had enlarged spleens.

Park Ross[11] has made a detailed investigation in the area along the Mozambique river and examined some hundreds of children under 10 years. To give an idea of the violence of the malaria, he mentions the following figures. Of the children examined 53 per cent. had parasites, 82 per cent. had either parasites or pigmentation or a strong

mononuclear leucocytosis; 70 per cent. had an enlarged spleen, and blood examination proved that in 60 per cent. of the cases this enlargement was due to malaria.

Niamey, an important town on the Niger, has a malarial index of 66.6 per cent. mostly praecox.[12]

In *West Africa, Marcel Léger and Nogue*[13] found by blood examination that of 303 persons 144 had parasites (47 per cent.). (Plates XVII & XVIII).

In the *United States* in 1923 in 29 states with a population of about 85 millions, 137,544 cases of malaria were reported.[14]

Nuñez[15] mentions that *Deaderick* has compiled a record of 5,109,001 authentic cases of malaria, showing 148.055 deaths or a ratio of 2.89 per cent.

At Belize *(British Honduras)*[16] from June till October 1921, 85 per cent. of the soldiers of a detachment were infected. The splenic index for the natives was 76 per cent.

At *Suriname, C. Bonne*[17] estimates that of the bushnigger children 54 per cent. and of the adults 24 per cent. are infected. The rate for black miners is 56 per cent.

In the annual report on the number of deaths from infectious diseases 1919—1923 in the *Straits Settlements*[18] malaria stands first with 3977 cases in 1922 and 2438 in 1923. In the same year the the numbers for tubercolosis were 2966 and 2508.

At Thanh-Hoo *(N. Annam) Bouvier*[19] found in 2772 children 1,807 enlarged spleens and in 1,358 children under 6 years 534 infected by parasites.

In Del Carmen district[20] on the *Philippine Isles,* an investigation for the malaria in this district gave the following results:

	Percentage of persons infected with parasites
Pabalang	28.9
Prado	14.4
Pulungmasle	20.5
San Jose	23
Tucop	39.9

On a hacienda during a period of 115 days about 30 per cent. of the population had malaria, on another $33^1/_3$ per cent.

From *Palestine*[21] the following is reported:

In the year 1921 3.61 per cent. of all illness was malaria. In the year 1922 this figure was 2.25 per cent. In the same year 27.444 persons in the villages were treated for malaria.

Armenia[22] is similarly situated.

Photo Dr. J. W. S. Macfie, Liverpool

Plate XVII AFRICA Page 148

Oedema consequent upon malaria in Negro children on the Gold Coast

Photo Dr. J. W. S. Macfie, Liverpool

Plate XVIII AFRICA Page 148

Oedema consequent upon malaria in Negro children on the Gold Coast

In the settlements which are principally occupied by farmers, the malaria is extra ordinarily frequent, and the parasitic index for *Azerbeidjan*[23] was in December 1922:

Age	Index
1— 5 years	83.4 per cent.
6—10 „	77 „ „
11—15 „	60 „ „
16—40 „	40 „ „
above „	30 „ „

Concerning *Europe* we cite from a report of the League of Nations[24]:

"The malaria situation in Europe in 1923 is dominated by the formidable epidemic in Russia, where over $5^1/_2$ million cases, more than twice as many as during the previous year, were notified. The disease was greatly reduced, on the contrary, in Poland. Information for 1923 is, as yet, too scarce for the other important malarious area of Europe, the Mediterranean littoral with its river basins, to form an opinion as to its general trend there. Data are available for about half of the countries only, and are frequently incomplete".

We mention from the given numbers only here:

Kingdom of the Serbs, Croats and Slovenes ..	17,926
Spain (deaths)	1,262
Poland	4,771
Russia in Europe (without Ukraine)	4,484,062
Ukraine	459,842

while at Belgrade[25] of 1,881 persons examined, 898 were positive, which gives a proportion of 47.2 per cent. If the cases of enlargement of the spleen are added to this number, the percentage attains 69.40.

Investigation of malaria in *Dalmatia and Herzegovina*[26] in 1922 gave the following results for 2.667 persons examined:

District	Proportion of quartan fever
Opouzen	46 per cent.
Dernitch	62 „ „
Vidogne	60 „ „
Verpolie	62 „ „

The splenic examination made on schoolgoing children gave for 1836 children a proportion of 53.5 per cent. which had greatly enlarged spleens.

Disquieting figures are given out for *Russia*.

The following information was presented by *Dr. Dobreitzer*[27] on behalf of the Russian Health Commissariat at the Pan-Russian Malaria Congress at Moscow, February 3rd, 1925.

"The number of malaria cases reported during the first ten months of 1924 for the whole of Russia amounted to 5,352,349, that is to say, 410 cases per 10,000 inhabitants. This incidence is similar to that of 1923 (400 per 10,000) but about twice as large as before the war (216 per 10,000 inhabitants in 1913).

In the European areas of the Union 3,709,806 cases were registered during the ten months in question, that is to say, 376 per 10,000 inhabitants. In 1923 this figure was 353 for the same period; in 1913 it was 176,8.

The reported incidence of malaria in the different districts was as follows (cases per 10,000 inhabitants):

Lower Volga	1,092	Viatka-Vietluga	180
Northern Caucasus	881	Western Ukraine	146
Middle Volga	799	Yakut Republic	111
Ural	761	Central Industrial	100
Eastern Ukraine	670	Turkestan	91
Siberia	528	White Russia	50
Kirghiz Republic	322	North Eastern	48
Trans-Caucasia	303	Western	34
Central Black Earth	302	Far Eastern Republic	17
Crimea	215	North Western	8

If these figures are compared with those for 1923, it will be seen that the incidence of malaria has changed to a varying extent in the different districts.

It has decreased in the North-Eastern region (48 cases per 10,000 inhabitants in 1924 as against 199 in 1923), Central Industrial District (100 as against 287), Middle Volga district (799 as against 1,119) and the Lower Volga district (1,082 as against 1,412), that is to say, it has decreased in all districts where in 1923 it had the character of a very serious epidemic. This decrease is also recorded in Turkestan (91 cases in 1924 as against 177 in 1923) and also in Trans-Caucasia (303 in 1924 as against 490 in 1923).

No change was observed in the following districts: North-Western (Karelia), Western (Pskoff), Central Agricultural, Viatka-Vietluga, Northern Caucasus, Far Eastern and the Kirghiz Republic. A considerable increase is reported in the following districts: Urals (761 per 10,000 inhabitants in 1924 as against 379 in 1923), Siberia (528 as

against 253), Ukraine (366 as against 159), Crimea (215 as against 97) and Republic of White Russia (50 in 1924 as against 24 in 1923). It is seen that malaria has increased in the districts which were only slightly affected in 1923.

In a few districts only was the incidence in 1924 similar to that of 1913, *e.g.*, Western District, Central Agricultural District, Northern Caucasus, Crimea, White Russia.

In some districts the number of cases per 10,000 inhabitants was lower in 1924 than in 1913, namely in the North Western (8 in 1924 and 15 in 1913), Trans-Caucasia (303 and 659), Turkestan (91 and 230) and the Far Eastern Republic (17 in 1924 and 98 in 1913).

In all the other districts the incidence of malaria is much higher than before the war.

Monthly fluctuations in 1924.

The figures for the first four months of 1924 are higher than those for the corresponding months in 1923. From June the figures show adecline and are below those of 1923.

The decrease began in Northern Caucasia in June, on the Middle Volga in April, on the Lower Volga in February and in the North Eastern districts in January.

In the districts where an increase in malaria was observed in 1924, *i.e.*, in the Ukraine, the Urals and Siberia, the increase showed itself in January and continued throughout the year.

The maximum number of cases in 1922 occurred in September in 1923 in June and in 1924 in May, which was the month of maximum prevalence before the war.

Only three Governments form an exception to this rule, *i.e.*, Samara, Tsaritzyn and Astrakhan. In Samara there were two maximum periods, one in May and the other in September. In the greater part of Siberia the maximum occurred in June and in two Governments, *i.e.*, Altai and Novo-Nikolayevsk, in May. In the Kirghiz Republic the maximum occurred in June. Northern Caucasus had two maximum periods, in May and August, the autumn maximum being higher than that in the spring.

The Trans-Caucasian Republics also had two maxima, *i.e.*, in May and September.

Forms of malaria.

The returns from malaria stations for 1924 show a high frequency of the tropical forms throughout the entire country.

In Siberia they constituted 0.5 to 9.3 per cent. of the other forms,

in the Ural 6 per cent., in the Central Industrial district 15 per cent. (Moscow Government 7 per cent., Kazan 15 per cent., Saratoff 26 per cent., in certain districts as much as 50 per cent.), Volga district 17 per cent., Vladikavkas and Daghestan 22 per cent., Trans-Caucasia and Armenia 56 per cent.

The quartan form is only reported from the Volga district, Northern Caucasus and Trans-Caucasia. It has not been observed to any great extent in other districts.

The monthly curve of the various forms of malaria shows that the increase of *plasmodium vivax* occurs in March and April with a maximum in May. It then remains on the same level fairly constantly until September.

The tropical form increases in July and August, with a maximum in September.

The quartan form is irregularly distributed with a maximum from September to January.

The decline in malaria incidence corresponds to a lowered gravity of the clinical forms. The malignant forms observed in 1923 in Northern Russia and the Volga district did not appear in 1924. On the other hand, malignant forms were observed in districts where malaria increased in 1924, especially in the Urals and Siberia.

Mortality has diminished. The highest mortality occurred in Siberia and Northern Caucasus, where it was estimated at 1 per cent., in Astrakhan at 6 per cent., and in Trans-Caucasia at 5 per cent.

Notification.

Notification of malaria cases was better carried out in 1924 than in 1923, as a result of the work done by the malaria stations, the distribution of quinine and propaganda. The fact that the figures for 1924 are generally higher than those for 1923 may be explained by an improvement in the system of registration.

All cases, however, have not been reported. Notification is still defective in the country districts. Specialists consider that the ratios established for these districts should be multiplied by from one-half to ten.

M. Dobreitzer considers that the actual number of malaria cases would be obtained by doubling the number of reported cases, which would give about ten million for the first ten months of 1924.

The decline in the incidence of malaria may be attributed to various factors: periodicity of the epidemic, improvement in the economic situation and particularly in nourishment, the dryness of the summer, and measures of control. The fact that the maximum point of the

epidemic occurred in May may be considered as a favourable sign for 1925.

The age-groups most subject to attack were from 20 to 50 years, corresponding to the working age, and a considerable number of chronic cases still exist. The anopheles is common throughout the whole of Russia, and the tropical form of the problem is increased by the fact that famine reigns in certain districts. It is obvious, therefore, that continued efforts are necessary if malaria is to be reduced to its pre-war level in Russia".

The perfectly correct argument that the destruction of the mosquito would bring about the disappearance of malaria, gave rise in the beginning to the view that it actually would be possible, by this means, to eradicate the disease, and the magnificent results obtained by the reclamation of the Panama Canal zone seemed to prove this.

This method was applied thoroughly, especially in the *United States*, where the cost is no obstacle, and the population readily cooperates in enforcing measures which are likely to be of general benefit.

Numerous publications describe the different courses which were adopted. As a typical one we give here the description of a campaign in Illinois.[28]

"Some interesting particulars regarding a campaign against the malaria mosquito, initiated and carried out by engineers at the town of Carbondale, Illinois, were given in a paper recently read before the Illinois Society of Engineers, by Mr. *Harry F. Ferguson*, chief Engineer of the Illinois State Board of Health. The author explained that in the State of Illinois land drainage work had been carried out for a number of years, and that it had greatly decreased the amount of malaria. Although the economic saving from decreased sickness and death from malaria — or from other diseases which may have attacked persons weakened by malaria — was not, he said, generally taken into consideration in drainage projects, the result should be included among the benefits resulting from drainage. In some cases the economic saving from decreased illness had, he added, exceeded the direct cost of the drainage work.

Vital statistics for Jackson County, in which Carbondale is situated, show the occurrence of from 2700 to 3000 cases of malaria annually. Assuming that the economic loss is £ 20 per case, the total loss in that one county is some £ 50.000 to £ 60.000 annually. The £ 20 per case which includes doctor's bills, medicines

and loss in productive earnings by the patients, is considered by Mr. Ferguson to be a conservative amount. Even so, the figures indicate that the county could well afford to spend a large sum yearly in eliminating mosquito-breeding places.

In the spring of 1922 the municipal authorities of Carbondale arranged to undertake complete control of the malaria mosquito in an area including the town itself and a district extending ½ mile beyond the town limits. The State Board of Health assigned sanitary engineers to plan and supervise the work. This campaign was very successful in controlling not only the malaria mosquito but also the other kinds which are merely a nuisance due to their stinging. In 1921 the town had 267 cases of malaria, or 4.26 per cent. of the population affected. At the end of the season's work in 1922, a house-to-house canvass showed 19 cases or, 0.3 per cent. of the population affected. The local doctors estimated 54 cases, but even if that figure be accepted, the result of the one season's work was remarkable.

A study of the situation showed that the mosquito-breeding places within mosquito-flight distance, included 60 acres of swamps on the north, a lake of 40 acres on the south, a number of small ponds and about 6 miles of ditches and streams. In addition, there were a great number of rain barrels and open wells and cisterns. To drain the swamps the Illinois Central Railway Company excavated a drainage ditch nearly 2 miles long, the line being interested in reducing the continual sickness among its employees living at Carbondale. This ditch was excavated by means of exploding dynamite charges, the work costing much less and being done more rapidly than by hand, so that most of the swampy areas were drained before the height of the mosquito season. The lake was an ideal breeding place, as there was an abundant growth of weeds and pond lilies, together with grass around the shores. As a first step, the outlet was cut so as to lower the water-level about 18in. Then the bays were cleared of weeds and growth. During the season the edges and portions of the surface were oiled at intervals. All ditches and watercourses were cleared out, and were oiled once a week. That these measures established almost complete control of natural breeding places was proved by frequent inspection.

The most troublesome part of the campaign was the control of rain barrels, wells and cisterns, Of 664 open wells and cisterns, 391 were found to be breeding places in June, and these were cleared by stocking them with small fish — *gambusia* or top-minnows being employed for this purpose. Of 1031 rain barrels and

tubs, 830 were found to be breeding places, but by continual treatment and inspection, these were steadily reduced until practically perfect control had been obtained by the height of the mosquito season. The total cost of the work, including that done by the railway also the engineer's time and expenses, was about £ 850. It resulted in the prevention of at least 200 cases of malaria, and also relieved the mosquito nuisance. Estimating an economic loss of £ 20 for each case, as noted above, the net saving was at least £ 3150, or more than the entire cost of the permanent work and the seasonal work of inspection and treatment. Small expenditure in succeeding years will develop greater economic savings. Mr. Ferguson states that the results were so apparent as to lead the town to prepare for continuing the work this year, while a neighbouring city is planning to initiate similar control of the mosquito".

Concerning the beneficial results of drainage, it is reported that at *Carey Island*[29] it has been possible to make an area of 20 square miles of low lying coastal land, practically free from malaria by drainage, while in the *Malay States* [30] Sir *Malcolm Watson* has observed excellent results by a system of subsoil drainage. The malaria cases dropped from 6105 in 1914 to 10 in July 1923.

R.M.M. Mangkoewinoto[31] reports how, with simple measures of drainage, combined with quinine treatment in periods of acute outbreaks, malaria cases in the Tjihea plain, a notorious malarial focus in Java, decreased considerably. He estimates the cost at about 50 cents (Dutch currency; = 10 pence) per head of the population, and a report from *British India*[32] mentions that a tea estate lying in the Eastern Himalayas at about 3000 feet altitude, with porous soil, consisting of decomposed granite, was drained and the streams regulated. This was followed by reduction of the malaria rate.

It seems, nevertheless, that even drainage does not give the same good results everywhere. Thus a report concerning *Bengal* says[33]:

"*Malaria increases after drainage and diminishes after flushing*". It has been known for hundreds of years that the draining of swamps involves a grave risk of increasing malaria unless the work is done so thoroughly that the land will either grow dry crops or at least be fit for pasture. On the other hand, it has been known that swampy tracts may be freed from malaria by flushing them with an abundant supply of water.

Along with drainage other measures according to local conditions are proposed.

Thus, for instance, in *Transcaucasia*[34] the cultivation of rice has now been forbidden by the Commissariat of Public Health, on land near villages, roads, railway stations and railways, while in *Catalonia*[35] an executive commission appointed to deal with malaria, insists concurrently with other measures that over rice land the water shall always move at a rate faster than 10 metres a minute!

It is evident that such measures are impossible say, on the *Isle of Java*, which is very densely populated, and where people must live by rice-growing.

The destruction of mosquitos in a certain area, for instance by cutting down the undergrowth, looks very well in theory, but in practice it entails the greatest difficulties. This is shown in a report from the *Cameroon*[36]:

> Malaria is fought down not only by the quinine prophylaxis and mechanical prevention (mosquito gauze), usual amongst Europeans, but also by cutting down the undergrowth and high grasses, destroying of breeding places by chemical agents, and drainage.
>
> Cutting down in the Cameroon is attended by the most serious difficulties.

Surely, the more we study the question of the anti-malaria campaign, the more difficulties arise, as was mentioned by *Malcolm Watson*[37] at the 5th Biennial Congress held at Singapore, 1923:

> "We have hardly begun the great campaign against malaria yet — Different places require different methods of attack — a method successful in one place may aggravate the disease in another place. We do not know why one species of Anopheles is a carrier of malaria, and another, hardly to be distinguished from it, is not."

In *America*, the first expectation that drainage would bring the desired results, has not been realised.

Welch[38] notes the spectacular fall in malaria following the initiation of control work in *Alabama*, and the hope of its speedy extermination which followed. Now comes the discouraging discovery that nothing of the kind has ensued, and the realisation of the disconcerting magnitude of the subject. Following this *Le Prince* showed that major drainage does not necessarily reduce the prevalence of malaria.

Dowling[39] writes:

> "Theoretically, it is extremely easy to prevent the spread of malaria and the eradication of the breeding places of the Anopheles; practically, it is very difficult".

Concerning the situation in *Panama*[40] we hear that any relaxation

of vigilance in the Canal Zone means increased malarial incidence. Colon was at that time (1920) being annoyed by swarms of Anopheles attributable to a swamp two miles away, half of this distance being covered by open water.

We can, therefore, quite understand that besides sanitary measures, quinine treatment has been tried to secure the desired result. The well-known *C.-G. Bass*,[41] without entering into a discussion concerning the fundamental merits of both methods, thinks that for the present in the United States, attention should be concentrated on the rational treatment of germ-carriers.

In limited areas, anti-larval measures give excellent results, as does also quinine treatment of the reservoir of virus. The difficulties arise when it is sought to put down malaria in a vast country.

Further, *Bass* notes that during the last few years in the U. S. anti-larval measures have been applied to a surface of about 5,180 square kilometres. But the malaria-infested area of the U. S. exceeds half a million sq. k.m. The amount of money required to take up this work is enormous; compared to this rational quinine treatment demands a much smaller sum.

With regard to this *Bass*[42] said: "If all cases of malaria were treated clinically by proper doses during at least two months, till recovery, malaria would no longer be a problem".

At the International Congress of tropical medicine at Kingston in 1924 *Bass*[43] pointed emphatically to the necessity of a sufficiently long after-treatment of all cases of malaria, which come under medical control; not only for clinical reasons, but also because it results, through decrease of the protozoa, in a real lowering of the number of infected Anopheles. We recommend therefore the general adoption of a routine method which he had tried.

Fülleborn[43] (Hamburg) reports that a systematical treatment of all germ-carriers combined with that of the apparently healthy children, in German malaria areas, has given excellent results; besides it is easily applicable in schools,

The fact that the authorities in the U. S. do not hesitate to carry through even the most drastic measures, is illustrated by the following communication:

"*Dr. M. A. Hort*[44] described how, by a mixture of education and compulsion, the disease was successfully stamped out in several places. In one town for example, an order was issued that every man, woman and child should have the eight weeks' standard-treatment with quinine or should leave. This was applied in the spring of one year, when

about 30 malarial cases had been reported and the prospect of reaching the previous year's total seemed likely, when no less than 300 cases occurred in one lumber mill. During the summer months following the treatment, however, no further case of malaria was discovered, and similar good reports were received from other districts where this eight weeks' treatment was applied".

We are not told how the enforcement of this ukase was controlled, nor if unwilling citizens really left the town. According to this principle the most efficacious method for an anti-malarial campaign would be to depopulate a country. This would put an end to malaria once for all, but as is evident measures like these cannot be considered seriously.

But it is clear that everywhere in the last few years, besides hygiènic measures an extensive use of quinine is recommended.

Writing about malaria in the *Dutch East Indies*, *de Rook*[45] proposes: More intense quinine prophylaxy and cattle-sheds to catch the mosquitos, because complete eradication of their breeding-places is too costly, and *Hendriks*[46] lays much stress on quinine treatment which is most promising when carried out at the schools. (Plates XIX & XX).

In *Peru*, *Escomel*[47] obtained very good results with high doses of quinine in acute cases and small regular daily doses in chronic malaria or as a prophylactic measure.

Concerning *Suriname*, *Bonne* [17] writes:

"In a routine way I treated Javanese only during fever, and some days afterwards. It is clear that such a quinine treatment is not ideal, but under the particular circumstances it was the most practical, and malaria disappeared almost in two years.

This does not mean that the population had become normal again; the spleen enlargements for instance were not gone; and the possibility of infection for the Anopheles was not taken away, but absence from work through malaria was inconsiderable.

Malaria as an economic problem was no longer of any account.

The success of these simple measures, mosquito-catching and quinine treatment, proves that the originally unfavourable factors in Moengo were very unstable".

In an account of the malaria in *Madagascar*, *Clouard*[48] is not hopeful concerning anti-larval measures. The main difficulty is undoubtedly the close proximity between paddy land and habitations. He considers that quinine therapy is more likely to give good results if it can be pushed vigorously.

Experiences are the same in *Morocco* and *Algeria*.

Oberlé and Vialatte[49] find prophylactic quinine of very great utility if properly taken under supervision.

Plate XIX

DUTCH EAST INDIES

Photo Dr. Ch. Winckel, Weltevreden

Malaria examination during a malaria epidemic in North-Bantam

Plate XX

DUTCH EAST INDIES

Photo Dr. Ch. Winckel, Weltevreden

Distribution of quinine tablets and administration of injections during the malaria epidemic in North Bantam

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The campaign against malaria in *Morocco*[50] in 1922 includes prophylaxy applied to colonisation (medical advice obligatory for colonials concerning the choice of a site, hygienic measures before settlement, importance of small anti-larval work after the completion of these measures), prophylaxy applied to the natives, "State-quinine" (which has been given since July 1922, but which costs a lot of money and which should nevertheless be distributed profusely, in order to root out the virus reservoirs, the final aim of anti-malarial work); prophylaxy amongst the army of occupation (where prophylactic quinine has been applied thoroughly since 1917, and which shows a considerable decrease in the malarial morbidity, notwithstanding certain lapses in the application.

In 1917-1918 a third of the Spanish army in Morocco was immobilized by malaria; some 11,000 men spending 318,310 days in hospital.

In *French Morocco* admissions to hospital for malaria per 1000 effectives fell from 83.9 in 1913 to 13.1 in 1919. The figure for 1922 was 24.6.

The writers are convinced of the value of preventive quinine.

In *Algeria*[51] prophylactic quinine in a daily dose of 0.4 gram taken for 5 months in the year in the hills and 7 months on the coast, and all the year round at Halia was issued to 3,500 persons in 1921, 4000 in 1922 and 10,000 in 1923. Small anti-larval measures, mosquito-gauze, complete the hygienic measures. It is held that grave attacks have been prevented, cachexia lessened and mortality considerably diminished.

In *Algeria*[52] likewise as in *Morocco*[53] anti-malarial work consisted in hygienic measures, drainage work and small anti-larval work, but always combined with quinine distribution.

In *Palestine*[21] after the war, the Department of Public Health took up the campaign against the principal diseases, in the first place malaria.

The American Jewish Hadassah Medical Organisation with plenty of material and well-schooled personnel cooperated with the State.

They started with the most important drainage works in different places, kerosene application and control of water-cells. In this way they succeeded in making the towns almost completely free of malaria. In the country and villages it was not so easy to destroy malaria altogether. In addition, quinine was given gratis and the population was instructed in this matter as much as possible by popular illustrated pamphlets.

While in Jerusalem[54] there were in 1918 still 113 death cases from

malaria, this number dropped in 1922 to 5. This was a result of the work of the above mentioned organisation.

It seems that in Palestine sanitation-work has done a lot of good. The anti-malaria committee reports:[55]

"In certain districts, however, and in all towns, the diminution of malaria was chiefly due to the measures taken to deal with the disease. This was particularly the case in the Jezreel Valley, where the extensive drainage works had brought about a most striking fall in the incidence of primary malaria among the settlers".

It is noticed that the fitting of pumps to water supplies is one of the standard sanitary measures used in Palestine. It will be interesting to know whether these are an entire success. Experience in the tropics shows that unless they become the private property of an individual they do not last very long; the treatment received at the hands of the public very rapidly renders them useless.

Its opinion concerning prophylactic quinine is not so favorable.

While treatment of carriers is an important element in malaria control it cannot be employed in Palestine as the sole measure because of the lack of a homogeneous population. When only a portion of the population can be effectively treated the fight against the parasite is incomplete and is at best only of limited value.[56]

Quinine prophylaxy was useful in reducing malaria morbidity during the period of relatively low incidence. During the epidemic period, even double the usual 5 grain dose was not effective in preventing new infections.

In the same way *Bylmer and de Rook*[57] report:

"During an exploration of the central highland of *New Guinea* malaria cases occurred within a fortnight after arrival, and within six months 96 per cent. of a group of 79 native soldiers were infected. In new batches of soldiers the epidemic ran a similar course.

Quinine prophylaxy, systematically carried out from the beginning (2 days a week 0.8 gram, later 0.4 gram every day, afterwards 2 days a week 1 gram) did not prove a success in preventing infection, but generally the attacks were of a benign character, which was ascribed to the quinine prophylaxy. Eleven cases of blackwater-fever occurred at outposts where quinine prophylay was neglected. *Bylmer* thinks that blackwater-fever can be prevented by a methodical treatment and early evacuation of persistent malaria cases".

Amongst the antagonists of quinine prophylaxy, *Kligler*[58] must be mentioned. Treating an epidemic of malaria in a camp in *Phoenicia* led him to the following conclusions:

"If prophylactic quinine reduces the number of cases, it has no prophylactic value, viewed from a public health point of view; it increases the number of latent germ-carriers, who spread the disease and also the number of chronic cases of malaria, which are very resistent to quinine. We may ask indeed whether a germ-carrier, camouflaged by quinine, is not more dangerous than a sufferer under observation, and finally whether prophylactic quinine does not possess more drawbacks than advantages".

Legendre[59] is practically of the same opinion.

Quite of a contrary opinion, however, is Maj. *Trabaud*, the writer of an article reproduced under the title: "*De l'intangibilité du dogme de la quinine préventive et du camouflage du paludisme par cette mesure de prophylaxie.*" (p. 63).

Comparing this further with the publication of *Visbecq and Lacaze*[60] on the importance of prophylactic quinine, we observe how diametrically opposed the opinions about the value of this measure still are.

Preventive quinine treatment of troops.

The object of this measure is, by means of the regular absorption of quinine, to provide an environment unfavourable to the development of the hematozoa introduced into the blood of man.

The method has been severely attacked. Therefore it is necessary before we go any farther, to set out our views regarding its efficacy.

After the great experience of three years stay, in Macedonia, of the biggest expeditionary force which ever existed, the value of preventive quinine treatment should no longer in our view be contested, above all by doctors.

Detractors of preventive quinine treatment put forward the following, among other usual arguments, against the method:

1. That it is inoperative. This is a mere assertion which makes all comment superfluous and which does not even possess the value of a hypothesis;

2. That it is injurious by its direct effect on the organism. It gives rise — so they allege — to gastric trouble and produces a predisposition to hemoglobinuric bilious fever. The experience of three years disposed of this opinion in Macedonia.

3. That it is injurious indirectly in the sense that it reduces the hematozoa resistent to quinine, or by causing habituation of the organism the result of which is that the ordinary doses would have to be exceeded when a therapeutic effect is to be obtained. This is a merely imaginative view which is not based on any pre-

cise fact. On the contrary, there are many doctors who, strongly in favour of the 3 gram dose two years ago, have become advocates of smaller doses (2 grams for instance), because they have perceived that these doses were sufficient. Exactly the opposite should have taken place if the above allegation were true.

4. That it transforms the clinical complex of symptoms of malaria, by shading off or masking the habitual reactions of the organism. Owing to this fact it is said malaria readily passes unperceived and leads the patient direct to anaemia and cachexy.

This latter argument falls to the ground for the following reasons: in the first place the figure of evacuations to the sanitary formations in respect of malaria decreased progressively every year in the army of the East. This contributed greatly to the maintenance of effectives.

Furthermore, examination for germ-carriers during the period January-August 1918, carried out on 1,500 soldiers in various regiments or units, gave a positive percentage of 4 which proves that their number is not considerable. All that could then be supposed is that the alleged malarial patients with masked symptoms have few or no hemetozoa (gametes) in their peripherial blood; but to say this is to agree to the incontestable collective efficacy of the method: the number of carriers of gametes being less, the chances of contamination are less and the condition of health of the troops as a whole shows the effect; a great forward stride is made in the reduction of the reservoir of military virus which every year spreads farther and farther among the troops.

On what can the allegations of the detractors of preventive quinine treatment be based in a general way?

1. On arguments by analogy, which can have nothing more than the value of a hypothesis.

2. On arguments created for the purposes of the cause:

a. In order to cloak regrettable ignorance by the pretentious affirmation of a personal conviction;

b. To give an excuse to idleness because the application of preventive quinine treatment requires constant vigilance and action;

c. To evade punishment by sheltering negligence under the authority of a theory;

d. To avoid suspicion of lack of foresight when the necessary stock of quinine has not been provided in time.

3. On medical-philosophical theories without scientific, clinical or experimental basis.

The appearance of these theories is always to be anticipated in

a country where the sun favours imaginative exaltation. They existed in Macedonia, but to the honour of the Medical Corps be it said, their advocates were rare. We need not dwell longer on this point.

The best that can be said of these purely imaginative views which, like weeds, must never be regarded with contempt but which should receive careful attention in order to clear them away, is that they are based on personal statistics which are often just extensive enough to put into a ridiculous light the person who, viewing them as wholly reliable, has put too hasty an interpretation upon them.

Furthermore such statistics, prepared amid the calmness of a unit or a formation, possess a value the scope of which should not go beyond the limits within which they were determined.

It is impossible to argue about the question of preventive quinine treatment just as freely and easily as one argues on a philosophical question.

One needs to have instituted the method on a large scale, checked its execution and observed its immediate and remote effects in order to form an idea of its advantages and drawbacks.

Ravaut showed that in the hospital departments where quinine administered *per os*, for curative purposes, was ineffective, the reason was that it is not taken. If this fraud is difficult to prevent in a hospital, it is much more difficult in the case of preventive quinine treatment in a unit where the individuals escape still more the direct action of the doctor. Before inveighing against the method it is therefore indispensable to make sure otherwise than by the simple assertion of the parties concerned, that the orders given have been strictly carried out.

In matters of epidemiology amid a wide population, where it is desired to determine the efficacy of a measure of general prophylaxy, one must guard against any hypothesis, any preconceived idea. The epidemiologist will, so long as it is necessary, confine himself to the role, somewhat prosaic perhaps but very fertile in useful information, of searching for and examining facts. He will go about a good deal, will see as much as he can for himself, will not allow himself to be influenced by the opinions which others will not fail to spread out before him to prove that they "know" the question; he will see everything on the spot and for that purpose it is necessary that he should be thoroughly at home in his business, that he should know how to "see". The motto of *Bertillon* is singularly true in this particular case: "The eyes can only see that which one knows and one only knows that which one always

has in mind". In order to know, one must have learnt and this kind of prophylaxy is a speciality, "a craft" which is learnt like others, by practise and not from manuals.

When the epidemiologist has collected all the necessary information on the spot, when he has studied all the elements of practical application, when, in a word, he has gathered an assemblage of facts in sufficient number, observed at length and subjected to severe criticism, then only, will he be in a position and entitled to pronounce an opinion to which faith may be given".

In *Italy*, the classic malaria-country, "State quinine" is distributed, combined with hygienic work. (Plates XXI & XXII).

The preventive measures against malaria comprise[61]: 1. compulsory notification; 2. regulation of surface water; 3. certain adaptions of dwellings and dwellers; and 4. the State issue of quinine. Attention is drawn to the remarkable results claimed for the railways by anti-malarial measures. Many compulsory measures are carried out by persuasion through voluntary societies (Red Cross), with State aid. The net result has been a fall in the deaths caused by malaria, from 70 per 100,000 in 1887 to 7 per 100,000 in 1914.

In *Tuscany*[62] a condition existed, defined as "paludism and anopheles without malaria", up to 1918. The experiences of the people led to their ready acceptance of quinine prophylaxy and treatment in 1922 and 1923. The maximum incidence in the latter year was 44 cases in May and but 2 cases in November, and none in December. It is advised that these anti-malarial measures should be continued.

In the Island of *Corsica*[63] after several unsuccessful endeavours, the following method for fighting the mosquito was proposed: regulation of the rivers and drainage of marshes. Next to this a systematically imposed treatment of the population with quinine, by officially schooled and controlled "distributors".

In the province of Caceres *(Spain)*[64] in 1922 the number of newly infected cases of malaria has been inferior to half the corresponding number for the previous year. The total number of fever cases decreased in a less degree (22 and 14). The endemic gave in Talayuela a number which was in proportion a third of that in the spice culture. In the adjoining areas of Talayuela the number of cases has slightly decreased, a result which is the more remarkable, because only therapeutic means have been used and above all because the population is very unstable.

Mention is made here of 2388 cases of malaria, the quantity of quinine used was 41,372 grams.

Plate XXI ITALY *Photo Prof. Dr. B. Gosio, Roma*

Splenomegalia in a boy in consequence of malaria Page 164

Plate XXII ITALY *Photo Prof. Dr. B. Gosio, Roma*

The same boy after treatment Page 164

The fact that social factors, and more particularly the standard of living of the population, play an important role in this matter, and especially that the resistance against the effects of chronic malaria increases in proportion to the raising of this standard is illustrated by a communication of *Sénévet*[65], who reports:

> "that the disappearance of malaria in the Double (Dordogne) seems to be caused by the decreased number of breeding-places for the Anopheles, a more general use of quinine and above all by a general improvement of the standard of living".

In *Dalmatia*, which is considered one of the malarial countries of Europe the measures adopted are[26]: fight against: 1. germ-carriers by quinine; 2. flying Anopheles by education of the population, and the use of insecticides and gauze; 3. the breeding places (filling up, clearing, drainage, reclamations, destruction of larvae).

The Board of Public Health and Social Welfare in *Roumania*[66] reports that Roumania nowadays is certainly one of the most infested regions of Europe. The Public Health Service not being able to fight the malaria by main drainage, land drainage and other sanitation works tried the sterilisation of the infested areas by the use of quinine in 1904 for the first time.

The results were very satisfactory. All who took the quinine treatment, kept free from fever till the close of the campaign.

Generally the experiments with prophylactic quinine in the village Belitori (in the department of Teleorman) have been successful.

> Dr. *Gorasco* concludes: "For us in the proximity of lakes and marshes, prophylactic quinine is the surest means to fight malaria.
>
> We have not yet started with the destruction of mosquitos. Sufficiently instructed officials as well as the money to cover the expences are wanting.
>
> The only hope for us is quinine prophylaxy. But looking to the future our hope lies in drainage and sanitation work, etc.
>
> When we consider that for Moldavia and the Banks of the Danube, 1,137,992 hectares belong to the flooded area, one understands that the necessary expenses for making this surface healthy are of little account, compared with the enormous advantages (in arable land and improvement of general health) which would be the result".

The Soviet Government in *Russia* has done its utmost to fight the stupendous epidemic of malaria which devastates that country. Sanitation work on a large scale is, for the present, out of question on account of the extent of the area and the lack of money. An anti-malaria service has been created with over 100 centres to distribute

quinine, together with a propaganda among the population regarding the importance of malaria and the way to fight it.

In 1921 obligatory notification of malaria was introduced.[67] Besides this, in Moscow in 1920, an Institute for the study of tropical diseases was established under the direction of Prof. *Marzinowsky*, while in 1914 the Council of People's Commissaries drew up an extensive scheme of measures against malaria.

The People's Commissariat for the Medical Service also published a series of rules and regulations respecting this, of which we may mention that under No. 10: "Instructions for the preventive administration of quinine".

Finally, we quote from the above mentioned publication of *Dr. Dobreitzer*, page 70:

"The shortage of quinine in the country is one of the principal obstacles encountered in the struggle against malaria. During the blockade Russia was almost entirely without it. This in part explains the enormous accumulation of malarial sufferers and the extraordinary growth undergone by the disease of late years. In 1922 there were imported 8000 kilograms of quinine, in 1923, 12,000; in 1924 it is proposed to import 60.000. Now the quantity of quinine required is enormous. If we estimate merely at 20 grams the annual quantity of quinine necessary for each malarial sufferer, it is found that in order to treat 12,000,000 cases the Union of Soviet Republics needs 240,000 kilograms".

As regards the importance of the epidemic *Mackenzie*[68] says:

> "The effect of the epidemic on the future of Russia will probably prove to be greater than that of the Revolution. From a healthy country inhabited by a virile energetic peasant population and entirely non-malarial throughout its greater extent, the whole of South Russia is now probably the most malarial country in the world. It is probable that a great degeneration comparable with the effect of malaria on ancient Greece will in the next 20 years alter the type of the whole population of these Cossack districts and will threaten to overwhelm the rest of Russia."

The same author in another publication[69] says:

> "Large sanitation works are for the present impossible, but at least quinine should be supplied".

The mission of the Society of Friends of whom the author is a member, has partly organised the anti-malarial work. A central bacteriological laboratory with sub-laboratories has been created and dispensaries which administer quinine locally. But even this is of

small importance compared with the vastness of the infected area. Distribution of quinine has to be very strictly supervised.

In another instance[68] this writer states:

"In wide distribution of quinine lies the only hope".

The Bulletin of the Committee of Public Health[70] reports:

"The fight against malaria is severely handicapped through lack of quinine, laboratory material and medical aid".

These difficulties which the Soviet Government has to overcome are illustrated in an article: *Seuchen und-Seuchenbekämpfung in Russland*[71]:

"A well arranged campaign against malaria as well as proper sanitation work have only been planned of late, owing to the fight against typhus which was considered to be of greater importance.

But under the supervision of experts like *Marzinowsky* (Moscow) and *Schingarowa* (Leningrad) the Soviet Board of Health has now taken up the fight. When it becomes possible for the Committee of Public Health to procure sufficient quinine and money, the enormous task of fighting the malaria in Russia, will be accomplished".

Concerning the results *Ethel M. Christie*[72] mentions:

"The Society of Friends sent a unit to the Buzuluk district in the famine area. Typhus claimed most victims during the winter and spring of 1921-22 but during the summer months there was an epidemic of malaria of an unusual seriousness. The death rate was appalling. Measures consisted in the free distribution of quinine. Patients had to attend at the clinic daily or as required to take quinine. This work was afterwards extented to the villages in the neighbourhood.

The results for Buzuluk only show that in a year the average of recorded relapses and re-infections was 5 per cent. with the safe supposition that the real average was not above 10 per cent.

Extensive sanitary measures were not taken".

Conclusion. The data here given show that the fight against malaria must not be based exclusively on sanitation work only; nor exclusively on the distribution of quinine. Only from a combination of both methods can the desired result be expected. Which of the two shall be preponderant is entirely dependent on local conditions; but it may be said for the present that for large areas with a dominant rural population the distribution of quinine, combined with small anti-larval measures, is the most economical way in regard to the expenses, while, at the same time, it gives a direct result.

Variis modis bene fit (et male), a favourite phrase of a well-known

Dutch physician, may also be taken as a motto for anti-malaria work; the last word has not yet been spoken; it even looks as if we are only at the beginning of the way which will lead us to the solution of the problem.

If we may take the plough as a symbol of sanitation work, we can condense the present state of this question in the words:

"ARATRO ET QUINA".

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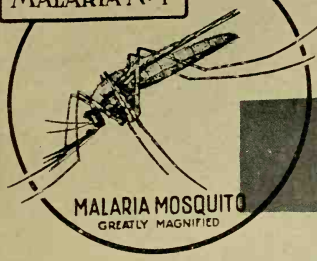
65 *G. Sénévet*, Le paludisme dans la Double (Dordogne). *Arch. Inst. Pasteur d'Algérie*, **11,** 1923-1924, p. 604.

66 Paludisme en Roumanie. Ministère de la santé et de la prévoyance sociale. Bucarest, 1924.

67 *A. J. Dobreitzer*, Le paludisme en Russie des Sovjets. Moscou, 1924.
68 *Melville D. Mackenzie*, Notes on the epidemiology of malaria in South-East Russia. *Lancet*, Dec. 8, 1923, p. 1225.
69 —— La lutte contre la paludisme en Russie. *Vers la Santé*, **5**, No. 1. Janv. 1924, p. 15.
70 Malaria und Malariabekämpfung in Russland. *Bulletin des Volkskommissariats für Gesundheitswesen*, No. 20, 15 Okt. 1923.
71 *C. Seyfarth*, Seuchen und Seuchenbekämpfung in Russland. *Zeitschr. f. klin. Med.* **100**, No. 1-4, 15 Mai 1924, p. 203.
72 *Ethel M. Christie*, An account of the malaria work done in Buzuluk Ooyezd by the Society of Friends. *Jl. trop. med. & hyg.* **27**, No. 13, July 1, 1924, p. 187.

I—XII. Posters concerning malaria as used in:
I. British India
II—V. United States of America
VI. The Dutch East Indies (sketch)
VII. The Dutch East Indies (sketch for pictorial school chart to be used for instructing native children)
VIII. Algeria
IX. Algeria (sketch)
X. France
XI. Roumania
XII. Russia

MALARIA № 1



The MOSQUITO DANGER

Mosquitoes suck Malarial Fever from Malaria Victims and carry the infection to sound and healthy people by biting them.

THE REMEDY

The Breadwinner down with Malaria, money gone, family starving.

मलेरिया बुखारसे बेकाम हुआ, धन खत्म हुआ, कुटुंब भूखों मरने लगा।

کمانے والا ملیریا میں مبتلا ہو گیا، روپیہ ختم ہو گیا، کنبہ فاقہ کر رہا ہے۔

Wife selling her ornaments, stopped by wise man who sent for Doctor.

उसकी स्त्री गहने बेच डालने का विचार किया, भला आदमीने उसको रोका और डाक्टर को बुला भेजा।

بیوی اپنے زیورات بیچ رہی تھی کہ عقلمند آدمی نے منع کیا اور ڈاکٹر کو بلا لیا

Doctor administered Quinine.

डाक्टर कुनैनाइन खाने को।

ڈاکٹر نے کونین بتلایا

Patient recovered. Wife and Children happy

वह बिमारसे अच्छा होगया, उस उसके स्त्री बैठे साथ रहते खुश हैं।

مریض اچھا ہو گیا بیوی بچے سکھی ہیں

Quinine is the only remedy for Malaria. Obtain it from Doctor, Post Office or Village.

कुनैनाइन मलेरिया कि एक ही दवा है। यह डाक्टरी के पास, डाकखाने या गांव के लोगों से।

کونین ملیریا کی ایک ہی دوا ہے اسے ڈاکٹر یا ڈاکخانے یا گاؤں کے لوگ سے لیں

The man who refused Quinine.

वह आदमी कुनैनाइन खाना अस्वीकार करी किया।

جس آدمی نے کونین سے انکار کیا

QUININE THE REMEDY FOR MALARIA

کرنین ملیریا کا علاج ہے

कुनैनाइन मलेरिया का इलाज है।

Plate I. BRITISH INDIA

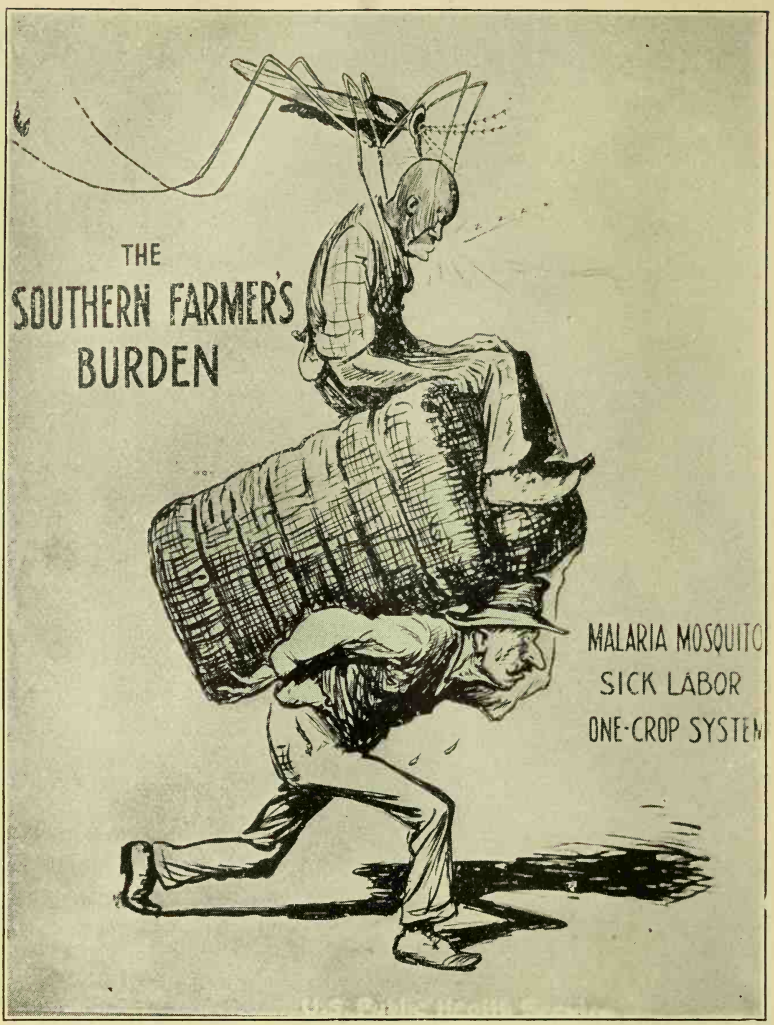
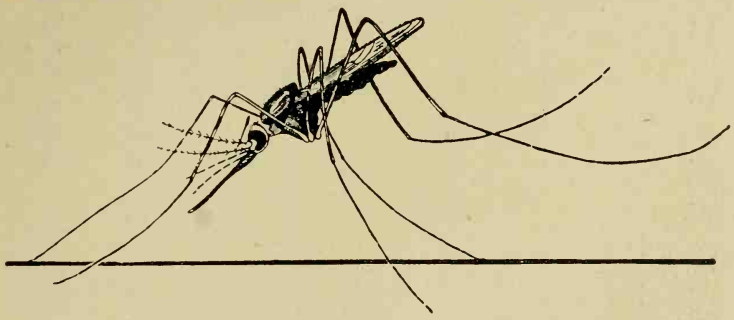


Plate II. UNITED STATES OF AMERICA

MALARIA



CURED BY

QUININE

TAKE THE STANDARD TREATMENT

SEE YOUR PHYSICIAN

MISS. STATE BOARD OF HEALTH

Plate III. UNITED STATES OF AMERICA

Standard Treatment For Malaria

(Chills and Fever)

Take 10 Grains of Quinine Sulphate by Mouth 3 Times a Day for 3 Days, Followed by 10 Grains Every night before retiring for 8 Weeks

FOR CHILDREN

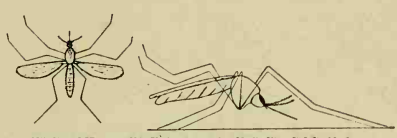
Under 1 year, 1-2 grain
1 year, 1 grain
2 years, 2 grains
3-4 years, 3 grains
5, 6, 7, years 4 grains
8, 9, 10 years, 6 grains
11, 12, 13, 14, years, 8 grains
15 years or older 10 grains

SOUTH CAROLINA STATE BOARD OF HEALTH

The State Co., Columbia, S. C.

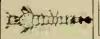
1923 – MOSQUITO CALENDAR – 1923
MISSISSIPPI STATE BOARD OF HEALTH

ANOPHELES MOSQUITO. THIS IS THE KIND THAT TRANSMITS MALARIA FEVER NOTE HOW IT STANDS – HEAD DOWN WITH BODY ELEVATED. THERE ARE SPOTS ON ITS WINGS



COMMON VARIETY OF MOSQUITO GENERALLY CALLED CULEX. THIS CLASS IS RESPONSIBLE FOR THE TRANSMISSION OF YELLOW FEVER AND DENGUE. NOTE HOW THIS MOSQUITO STANDS – LIKE A FLY. ITS WINGS ARE CLEAR

ANOPHELES PUPAE



ANOPHELES LARVAE

ANOPHELES EGGS

THE FEMALE ANOPHELES MOSQUITO LAYS ITS EGGS ON WATER. SHE SELECTS THE SHADED, GRASSY EDGES OF SLOW-MOVING STREAMS, PONDS, AND SOMETIMES STAGNANT WATER CONTAINERS. THE EGGS WHICH ARE LAYED SINGLY, ARE GLUED TOGETHER AND FLOAT ABOUT LIKE SPECKS OF DUST UNTIL THEY HATCH INTO THE WIGGLE MOSQUITO.

MALARIA FEVER IS TRANSMITTED ONLY BY THIS MOSQUITO. SHE GETS THE MALARIA PARASITE OR GERM BY BITING SOMEONE WHO HAS MALARIA. THIS PARASITE UNDERGOES CERTAIN CHANGES IN THE MOSQUITO'S BODY AND IS INJECTED INTO THE BLOOD OF ANOTHER PERSON WHEN THE MOSQUITO BITES THEM.

MOSQUITOES LIVE FOR MONTHS.

ONLY THE FEMALE MOSQUITO BITES.

CULEX PUPAE

CULEX LARVAE

CULEX EGGS

THE COMMON MOSQUITO AS CULEX, DEVELOPS IN THE SAME MANNER AS THE ANOPHELES. BUT THE FEMALE DOES NOT LAY HER EGGS IN RAFTS, AND FLOATS ON THE WATER AS SHOWN ABOVE. THE EGGS OF THE ANOPHELES ARE SEPARATED, THE LARVAE AND PUPAE OF MOSQUITOES ARE SHOWN ABOVE. THE SMALL WHITE COMMA-LIKE THE WATERS SURFACE. THE CULEX LARVAE HANGS WITH ITS HEAD DOWN. THE ANOPHELES LARVAE LIES PARALLEL TO THE WATERS SURFACE. BOTH LARVAE FEED ON THE SURFACE GERMS AND THE ANOPHELES LARVAE WIGGLES ACROSS THE SURFACE.

CULEX MOSQUITOES FIND LITTLE DIFFICULTY IN TO BREEDING PLACE. CERTAIN VARIETIES OF THEM WILL BE FOUND BREEDING IN SWAMPS, STAGNANT BREEDS, RIVERS, PONDS, LAKES, TIN CANS, HOLES, TOP OF TREES, TIN TANKS, ETC, ETC.

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OCTOBER						
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NOVEMBER						
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DECEMBER						
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23/30	24/31	25	26	27	28	29

DRAIN

OIL ON WATER KILLS MOSQUITO LARVAE AND PUPAE

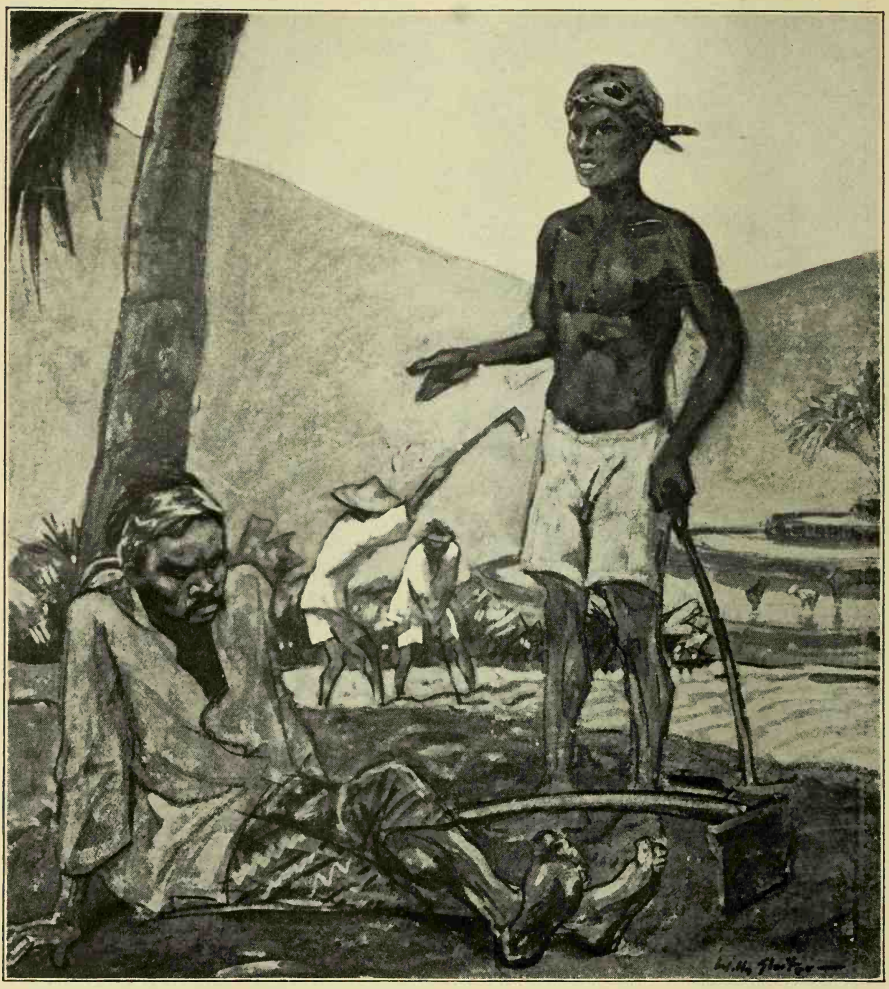
FOUR METHODS FOR CONTROLLING MOSQUITOES

TOP MINNOWS EAT MOSQUITO LARVAE

SCREEN

GEORGE PARKER, SANITARY ENGINEER, MISSISSIPPI STATE BOARD OF HEALTH.

Plate V. UNITED STATES OF AMERICA



SAKIT DEMAM. SALAHNJA SENDIRI.
KENAPA IJA TIADA MAKAN TABLET-KININE SAPERTI SAJA.

(Are you suffering from fever? It is your own fault.
Why don't you take quinine tablets, as I do?)

Plate VI. THE DUTCH EAST INDIES

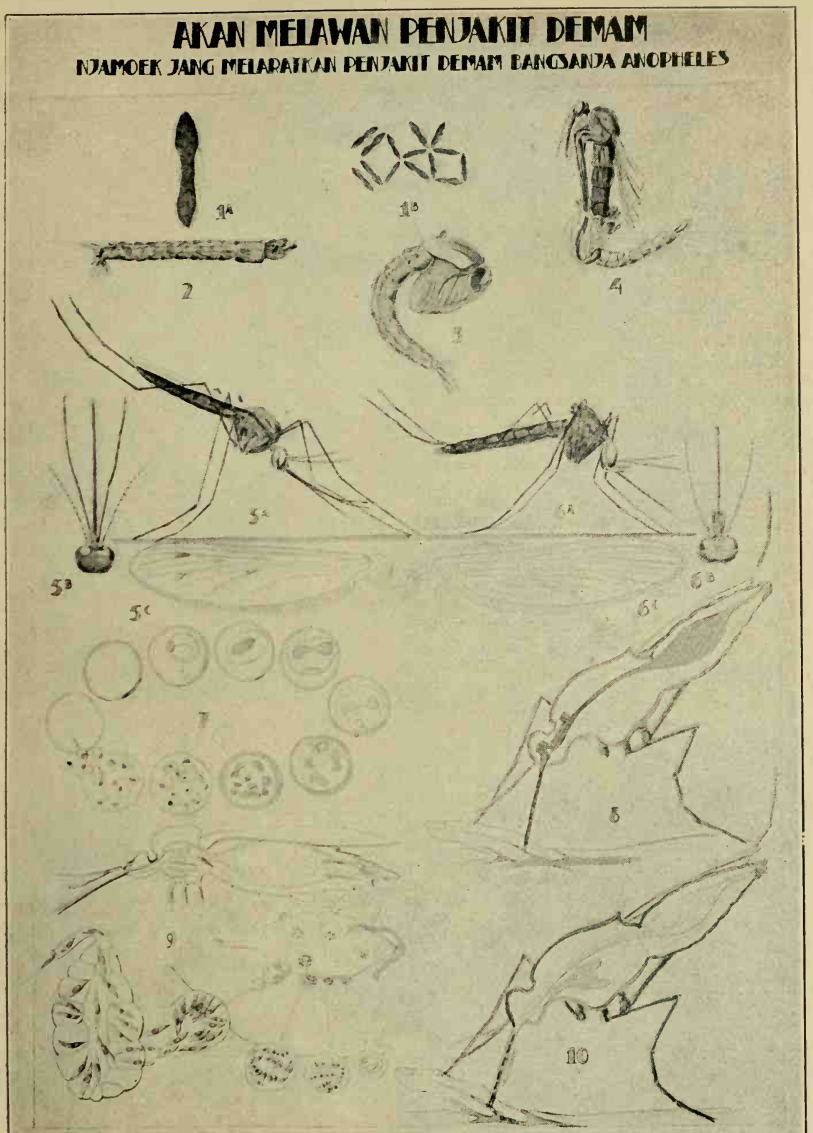


Plate VII. THE DUTCH EAST INDIES

CONTRE LES FIÈVRES PALUDÉENNES

— Les fièvres paludéennes sont propagées par la piqûre de certains Moustiques : les *Anopheles*.

— La destruction des Moustiques par le *pétrolage* des eaux stagnantes, la protection par les *moustiquaires* sont donc des moyens d'éviter les fièvres.

— Dans les pays paludéens, il est bon de prendre *tous les jours*, durant tout l'été, vingt centigrammes de quinine (c'est-à-dire une dragée rose du Service anti-paludique) : 1° Si l'on n'a jamais eu les fièvres, cette dose journalière agit *préventivement*, c'est-à-dire est destinée à empêcher l'infection ; 2° Si l'on est déjà fiévreux, cette dose journalière agit *curativement*, c'est-à-dire atténue la gravité des accès et amène la guérison complète.

إنّ الحمّيان نوفع من فرصة بعض الناموس بحيث يلزم الانسان
يحفظ نفسه من الحمّى ان يهلك الناموس بكبب نصيب بيترول
على الماء الرافدة و ان يستر روحه بالناموسيّة يلزم للانسان الساكن
في بلاد محموم ان يبلع حبّة من ٢٠ صانتيغرامًا من الكينه (يعنى الحبّة
الواردية من ولاية العمومية) كل يوم حبّة مادام الصيف و هذه الكينة
تحفظ من الحمّى الذي ما مرض منها و تبرأ الذي كان محـــــــوم

Recommandations de l'Institut Pasteur de Paris, publiées par les soins du Gouvernement général de l'Algérie.

Plate VIII. ALGERIA

مَعَك حُمَّى ؟ انت ظالم نفسك
لايش ما تستعمل أقراص القينه قينه مثلى أنا ؟

(Are you suffering from fever? It is your own fault.
Why don't you take quinine tablets, as I do?)

Plate IX. ALGERIA

Pour revenir en bonne santé

Ce sont certains Moustiques qui inoculent par leur piqûre le microbe du PALUDISME.

Au MOUSTIQUE
oppose la barrière de ta
MOUSTIQUAIRE

qui te permettra de bien te reposer, de dormir à l'abri des mouches et des moustiques. Soigne la moustiquaire. Apprends à la bien monter, à la bien border. Evite de la déchirer, répare les accrocs.

Comme tu peux être piqué en dehors de la moustiquaire :

au MICROBE
oppose la QUININE.

La quinine que tu avales va dans ton sang tuer le microbe; elle t'évitera la maladie ou la **rendra moins grave.**

PRENDS TOUS LES JOURS,

où que tu sois, quoi que tu fasses, les doses de quinine qui te seront données.

S. S. D'ÉTAT DU SERVICE DE SANTE
M. P. A. O., n° 9.

Imprimerie, 3, rue de Pondichéry, Paris. — 14424-5-16.

Plate X. FRANCE

FRIGURILE

(MALARIA)

Cum se iau?... Prin înțepături de țânțar

IN CE CHIP?

Țânțarul ia sămânța frigurilor dela omul bolnav și o duce la omul sănătos, îmbolnăvindu-l!

CUM NE FERIM DE FRIGURI?

Scăpând de țânțari!

Țânțarii își depun ouăle și se prăsesc numai în mlaștini, în băltoace și în orice apă stătătoare.

Deci:

1. Să nu faceți lângă casă, gropi în care să se adune apă.
2. Nu lăsați băltoacele în jurul puțurilor și fântânilor.
3. Desfundați șanțurile șoselelor, lăsând să se scurgă apele.
4. Țineți acoperite butoaiele cu apă.
5. Secătuiți mlaștinele și băltoacele, mai ales pe cele din apropierea locuințelor

Să ne ferim cât putem de împunsăturile țânțarilor.

Când nu putem să ne ferim de țânțari

Alungând țânțarii prin fum.
Prin pânze de tifon, sau sârmă deasă la uși și ferestre.
Stârpind cuiburile de țânțari din casă, prin fum de pucioasă sau de răsină

Toți acei ce trăiesc în satele bântuite de friguri și nu se pot feri de mușcăturile țânțarilor chiar când sunt sănătoși să ia chinină zilnic, câte 25 centigrame pentru copii și 40 centigrame oamenii mari, până ce țânțarii dispar.

CUM NE VINDECAM DE FRIGURI?

Numai chinina omoară sămânța frigurilor. Ca să lucreze bine chinina trebuie luată:

De către omul bolnav	1 gram pe zi (bărbații) 80 cent. gr. pe zi (femeile) 25 cent. gr. pe zi (copii)	Se va lua astfel până încetează frigurile

Dar nu este deajuns!

Ele pot să revină, de aceea chinina trebuie luată, chiar când nu te mai scutură frigurile; 3 săptămâni în șir de 3 ori pe săptămână aceeași cătime, apoi alte 3 săptămâni de câte 2 ori pe săptămână și apoi câte o singură dată pe săptămână până la 1 Decembrie.

Un țânțar (anofel)
MARIT

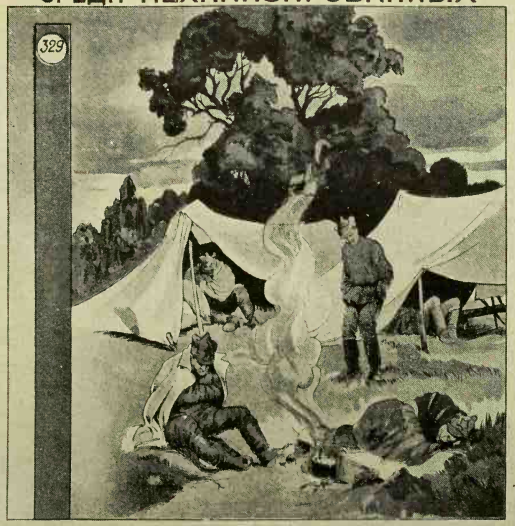
Direcția Propagandei:
Ministerul Sănătății Publice

Plate XI. ROUMANIA

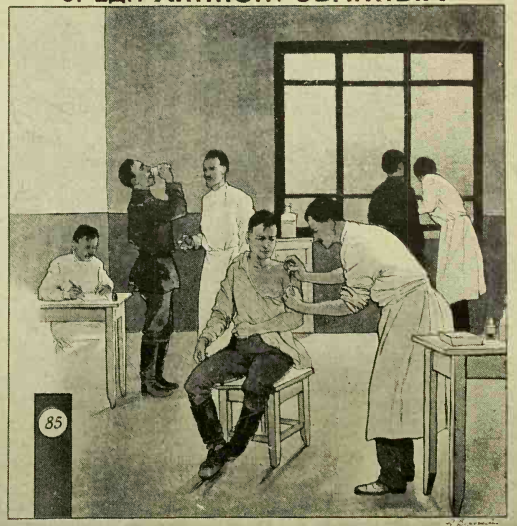
ХИНИН ПРЕДОХРАНЯЕТ и ИЗБАВЛЯЕТ ОТ МАЛЯРИИ.

В ВОЙСКАХ СКВО В 1922 г. НА КАЖДУЮ 1000 ЧЕЛОВЕК ЗАБОЛЕЛО МАЛЯРИЕЙ:

СРЕДИ НЕХИНИЗИРОВАННЫХ



СРЕДИ ХИНИЗИРОВАННЫХ



Quinine both prevents and expels malaria.
In the army divisions of SKWO in 1922, per 1000 men were suffering from malaria:
Not-quininised: 329 Quininised: 85

Plate XII. RUSSIA

SUBCUTANEOUS (INTRAMUSCULAR) QUININE TREATMENT IN LOBAR PNEUMONIA

LYDER NICOLAYSEN, CHRISTIANIA

From the VIII Medical Ward of the Ullevaal Hospital.

THE treatment of pneumonia by quinine is of old standing; it was first recommended in the seventies of last century, among others, by *Jürgensen*. He employed large doses with one day's interval and the object was to act on the fever. Quinine therapy came to occupy a somewhat different position after *Aufrecht* had introduced its subcutaneous use, as it seems that the effect differs materially according to whether the quinine is administered subcutaneously or per os.

Aufrecht[1] maintains that quinine has a specific effect on pneumonia and his view is that, by consistent use of quinine he has lowered the mortality. With the earlier treatment from 1885 to 1895, he had 1024 pneumonia cases with about 18 per cent. mortality. From 1895 to 1900 there were treated subcutaneously with quinine 382 cases with 8.4 per cent. mortality. If only the last preceding five years (1890—1895) were taken, throughout which the pneumonia showed low mortality, he had 512 cases with 14.5 per cent. mortality.

Cahn-Bronner[2] in the course of four years treated 344 cases, of which 156 received quinine, while 188 had no quinine, in order that they should serve as control. Those treated with quinine showed 6.4 per cent. mortality, while the control cases showed 25 per cent. or deducting those which were admitted moribund, 20 per cent. mortality. It further seems to follow from his statistics that the crisis in 60 per cent. of the cases treated at the very start of the disease occurred earlier than would have been expected, on comparison with the control cases. In one fourth of the cases he held that he had arrested the illness. In another work[3] his investigations were specially directed towards the object of determining the difference between administering quinine per os or subcutaneously. The result of these investigations tends to show that on cutaneous injection a quinine deposit is formed beneath the skin; by absorption from this deposit a much higher and

more persistent concentration of quinine in the blood is secured than by absorption from the intestine. After several injections cumulation occurs in the blood. Furthermore the quinine accumulates in the organs and can be demonstrated therein longer than in the blood.

The pneumonic infiltrated lung, 4 days after an injection, still contains quinine in a concentration which is higher than is ever found in the blood. Pneumonia sufferers eliminate quinine for a long time through the sputum.

Boecker[4] examined the constants of quinine in the lungs and expectorate in consumptives and found a strikingly large content of quinine in the lungs and sputum. Tests on guinea pigs also seem to show that the quinine is concentrated in the lungs.

In a lengthy survey[5] in 1922, *Cahn-Bronner* collected all observations and relevant literature. *M. John*[6] recommends quinine treatment after having tried it for six years on 197 cases; his mortality is nevertheless still high, namely: more than 19 per cent., as compared with 28.7 in cases treated outside the Hospital. As the Hospital moreover received the severest cases the difference possibly is greater than the figures appear to show.

The mortality from pneumonia both in and out of the Hospital varies considerably. It is throughout greater in women than in men, and, as is well known, increases with age.

According to the investigations of *Thiis*[7], during the decade 1895 to 1904, the mortality in the Krohgstøtten and Ullevaal Hospital was 28 per cent. of 260 cases during 10 years; if children under 10 years of age are included, he obtained a mortality of 27 per cent.; in men 18.3 per cent., and women 27.5 per cent.; as women formed four fifths of his material, their percentage of mortality will determine the results as a whole. The mortality in *Thiis's* material was: under 30 years about 10 per cent.; 30 to 40 years, 23.5 per cent.; over 60 years, more than 50 per cent.

In the years 1916-1917 in the three medical wards of the Ullevaal Hospital, 186 pneumonia cases were treated, with 25 per cent. mortality; of these 126 were men with 21 per cent., and 60 were women with 31 per cent. mortality. Judging from this, it would appear that the pneumonia mortality in the Hospital in Christiania has remained fairly uniform during the last decade.

Since July 1919 I have treated all pneumonia cases in the VIII ward with quinine. In order to form an idea of the effect of this treatment, I, for purposes of control, tried to compare the results of pneumonia treatment without quinine in the VII and IX wards, with the quinine treatment in the VIII. Owing to the kindness of the chief

physicians, *Scheel & Figenschau*, I was permitted to go through the lists of their wards. Admission into the three medical wards of Ullevaal is granted by the Medical Committee, which distributes the patients according as beds are available. The pneumonia cases may therefore be assumed to be throughout of the same kind in the different wards at a given time. If furthermore the distribution of ages and sexes is the same in the three wards, the conditions for judging the result of quinine treatment would be provided, namely: uniform material and a sufficiency of control cases.

The diagnosis can of course be made with lesser or greater certainty. Generally however, it may be assumed that the diagnosis of lobar pneumonia is made with great certainty and presumably equal certainty in the dfferent wards. A point which may be of some importance further, is whether an equally sharp distinction is made between lobar and catarrhal pneumonia, so as to exclude the latter form. For this and some other reasons it would, on the whole, be difficult to secure absolutely homogeneous material.

The years 1918 and 1919 were not made use of, in view of the influenzal pneumonia then prevalent which, judging from the literature, is not influenced by quinine and the differential diagnosis of which from lobar may occasion difficulty. The pneumonia cases here treated comprise the period from 1st January 1920 till 1st April 1923, that is $3^1/_4$ years.

During that period there were treated in the VII and IX wards 254 pneumonia patients, about 66 per cent. men and 33 per cent. women; in the VIII, 99 pneumonia patients, about 56 per cent. men and 43 per cent. women. In the VII and IX, about 48 per cent. were aged from 10-30, about 29 per cent. from 30-50 and about 22 per cent. over 50; in the VIII the percentages comprised in the same groups of age were respectively 45, 26 and 28. The material was therefore fairly alike as regards sex and age, with possibly some disadvantage to the VIII ward. If for the years mentioned mortality statistics are prepared according to the result of diagnosis for all three wards in the same way, it will have the following apect:

In the VII and IX wards during those $3^1/_4$ years there were treated 254 pneumonia patients, with 58 deaths = 22.8 per cent. mortality. During the same period there were treated in the VIII ward 99 pneumonia patients with 13 deaths = 13 per cent. mortality. Deducting the patients admitted moribund, that is to say, those who died within the first twenty-four hours and in whom the treatment applied cannot be considered to have played any material part, the following table can be drawn up:

		Treated		Deaths		Mortality
	Years	Men	Women	Men	Women	
VII & IX Wards	10—30	82	35	4	10	12.– p. ct.
	30—50	42	21	5	6	17.– ,,
	50—80	32	25	9	7	28.– ,,
	Total	156	81	18	23	17.3 p.ct.
VIII Ward	10—30	26	19	1	1	4.– ,,
	30—50	20	6	0	1	4.- ,,
	50—80	8	16	3	3	25.– ,,
	Total	54	41	4	5	9.4 p. ct.

As will be seen the individual groups in this table are very small and a couple more deaths in both instances would make a rapid change in the ratio. From the statistical point of view therefore it is hardly reliable and I only compiled it in order to show the distribution between sexes and ages. It is only the principal figures which can be used and which show that during the period, in the VII and IX Wards there were treated 237 pneumonia patients with 17.3 per cent. mortality, and in the VIII—95 pneumonia patients with 9.4 per cent. mortality.

If we try to distribute the material it may perhaps be permissible, and in any case not uninteresting, to lay down a dividing line at the age of 50; if this is done the following view results:

	Years	Treated	Deaths	Mortality
VII & IX Wards.. ..	10—50	.. 180	25	13.9 p. ct.
	50—80	.. 57	16	28.– ,,
VIII Ward	10—50	.. 71	3	4.2 ,,
	50—80	.. 24	6	25.– ,,

If there is any benefit obtainable from quinine treatment it appears likely to make itself manifest in pneumonia patients under 50 years of age.

As stated, these statistics have been prepared according to the lists in order to create the most uniform possible conditions, they start from the 1st January 1920. I had however, as far back as 1st July 1919, begun the quinine treatment and consequently I have treated with quinine a number of other cases besides those indicated above. If I deduct the deaths within the first twenty-four hours and also some instances in which the crisis followed almost immediately after the injection of quinine, and a couple of cases which received no quinine, I have, from the 1st July 1919 to the 1st July 1923, treated 130 pneumonia patients with 9 deaths = 6.9 per cent. This should therefore give a somewhat adequate expression of the mortality in pneu-

monia under quinine treatment when the material is sifted. If here likewise, a dividing line is put at 50, we obtain: 10—50 years, 99 pneumonia patients with 4 deaths = 4 per cent.; 50—80, 31 cases with 5 deaths = 16 per cent.

It might be of interest to examine the individual cases in which death supervened, and I therefore describe them with the utmost brevity.

Firstly the four cases under 50:

1. Man of 35, admitted at the beginning of 3rd day with pneumonia in upper right lobe; died on 5th day. Had had chronic alcoholism and delirium; post mortem showed fatty degeneration of the liver, heart and kidneys.

2. Girl of 15, admitted on 3rd day with pneumonia in lower left lobe; died on 8th day. No post mortem.

3. Man of 29, admitted on 3rd day with pneumonia in left lower lobe; died on 9th day. No post mortem.

4. Man of 36, admitted on 3rd day with pneumonia in left lower lobe; died on 7th day. Post mortem showed pneumonia in right lung and on the left side fibrinous pleurisy and fibrinous pericarditis.

The following five were over 50 years of age:

5. Man of 70, admitted on 10th day with pneumonia in entire right lung; died on 12th day. Post mortem showed pneumonia in entire right lung with total pleural adhesion, also an old tuberculous focus in the right lung.

6. Woman of 59, admitted at the end of the 6th day with pneumonia in whole of left lung and serpiginous syphilid on legs; died on 18th day. No post mortem.

7. Woman of 55, admitted on 4th day with pneumonia in whole of the right lung. Died on 9th day. Post mortem showed pneumonia in whole of right lung, splenic enlargement and parenchymatous degeneration of liver and kidneys.

8. Man 63 years, admitted on 4th (7th ?) day with pneumonia in whole of right lung. Died on 6th (9th ?) day. Post mortem showed pneumonia in whole of right lung, hypertrophy of the heart, shrivelled kidneys and luetic aorta with thrombosis in the aorta.

9. Man of 65, admitted on 2nd day with pneumonia in left upper lobe, died on 6th day. Post mortem showed pneumonia in left upper lobe, bronchitis, hypostasis and oedema in both lungs and parenchymatous degeneration of the kidneys with splenic enlargement.

As will be seen from the above the four patients under 50 years of age were treated in the course of the 3rd day of illness. No. 1 was complicated with alcoholism and was, to that extent, less favourable;

the remainder however could possibly have been saved if a specific action were in question. In case 4 the treatment was unable to prevent extension to other serous cavities, and in some of those who recovered empyema appeared. The five over fifty years of age were throughout severe cases of pneumonia which, in cases 5 and 6 and possibly 8, came under treatment rather late. But case 9 shows a medium, uncomplicated pneumonia which was treated on the 2nd day. In this case a specific medicine should have manifested its action. In any event it is not possible, from the individual cases of death, to make any deductions which may serve as a basis for pure statistics. In contrast to *Cahn-Bronner* I was unable to observe any reliable influence on the fever curve or its duration. The last mentioned writer believed himself able to prove statistically that the crisis, with quinine treatment, occurs earlier than otherwise. In order to settle such a question however, both his figures and mine are too few. To eliminate possible elements of chance much bigger figures would be needed. On the other hand a patient's general condition appears to be appreciably improved and it was our impression that the clinical picture is throughout more satisfactory during quinine treatment. On this point the majority of writers appear to be agreed.

There was used *Aufrecht's* formula:

Quinine hydrochloride	0.50
Urethane	0.25
Water	5.00

In this form, quinine can be given in a relatively concentrated solution which can be boiled. Should a little quinine be precipitated out it will be readily dissolved by heating the liquid. The injection is made intramuscularly in the nates or the thigh. Only in a few rare cases was there an infiltration of any duration, or slight necrosis. For the rest we saw no injurious effect. The patients were given one injection straightway on admission, on the following day and afterwards every second day, but as a rule not more than 4 injections. Together with this treatment they received camphor per os or subcutaneously.

If the quinine acts, then it stands to reason that the result will be better the sooner the disease comes under treatment, but it should be emphasized that it appears to have a beneficial effect in any stage of the illness. It is not easy, on the basis of the material on hand, to judge the benefit of quinine treatment, just as, on the whole, it is exceedingly difficult to determine the effect of a given agent in a disease having so relatively good a prognosis as lobar pneumonia. Even large figures might leave doubt here. But, taking into consideration

the fact that we have nothing much better to go by, I have found the results so encouraging that I feel myself strongly impelled to continue this treatment until some better one comes upon the scene.

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MODERN METHODS OF TREATING LOBAR PNEUMONIA

READ AT THE ANNUAL MEETING OF THE MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND, APRIL 26, 1923

HENRY M. THOMAS, JR., M.D., BALTIMORE, MD.

TO confine one's entire attention to the newer methods of treating lobar pneumonia would be to neglect the still most important aspects of the therapy of the disease. It is only necessary to look back over the almost countless list of discarded therapeutic measures to convince ourselves of the wisdom of the remark made by *Juergensen*, "Nature cures, and the only duty of the physician is to maintain life until this cure is effected".

Of late years the increase in knowlege of the etiological agents responsible for lobar pneumonia has led to an increased activity among therapeutists to develop specific forms of treatment. Specific sera, vaccines and chemicals all have their advocates and it is to these measures that we shall return after a brief consideration of the most important general methods.

General regimen in the care of pneumonia. The toxemia of lobar pneumonia is of a sharp, sudden, severe type seen in few other diseases. Lasting, as it ordinarily does, only about seven days, the necessity of building up the body tissues is not an important one. We must do nothing to interfere with elimination (by stopping up the bowels); otherwise we may feed as we like. On the other hand it is essential to increase every form of elimination possible and to this end fluid forced to 3 to 4000 cc daily, allows the kidneys, bowels and skin to function best in this respect. Should vomiting or delirium interfere with the fluid intake subcutaneous injections of salt solution or *Murphy* drips may be resorted to.

The severity of the toxemia is frequently revealed by a failing myocardium. We must spare no effort to relieve the heart muscle from the very onset of the disease. Of great importance in this respect

is the prevention of any movement on the part of the patient. This, in my opinion, is the most valuable contribution that can be made by the trained nurse. The patient must be lifted whenever he even so much as turns in bed. I know of four patients who have died while, or immediately after, using a bedpan. The physician should make this clear not only to the nurse but also to the patient, care being used, of course, not to alarm the latter unnecessarily. All forms of treatment which require exertion on the part of the patient must, therefore, be modified. Recent studies by *Levy* have shown that the digitalized heart does not dilate as readily during pneumonia as the undigitalized controls. This would seem to be sound argument for the early administration of digitalis. Certain it is, however, that digitalis in some form is urgently indicated at the first sign of myocardial insufficiency. The powdered leaves may be used by mouth but a more rapid and certain method of administration is digitalin or digifoline hypodermically. Sudden heart failure may require, in addition, the use of morphine and atropine or even venesection. Caffein (sodiobenzoate) and camphor (in oil) are stimulants to be used when necessary after the full amount of digitalis has been given or when additional stimulation is required.

The toxemia may also make itself felt on the peripheral circulation in the form of vasomotor paralyses and this is best combated, or rather best prevented, by hydrotherapy in the form of cold sponging every three or four hours. As cautioned before it is ill advised to move the patient and so the sponging may be confined to the anterior surface of the body and the extremities. Moving the patient into a tub is absolutely contra-indicated. Epinephrin or pituitrin are sometimes helpful in raising the blood-pressure by action on the peripheral vessels and strychnine may act by stimulating the medullary center.

Perhaps the commonest result of the severe toxemia is abdominal distention due to paralysis of the intestinal musculature. Few cases run the course of lobar pneumonia without at some time being disturbed by tympanitis and it should be anticipated and treatment instituted at the earliest moment. Turpentine stupes are often sufficient to relieve slight degrees of distention (hot turpentine stupes to be applied for twenty minutes and then replaced by hotwater stupes for twenty minutes and then the process repeated) especially if a rectal tube be inserted. More marked or persistent distention may require turpentine enemata (turpentine, 15 cc to 1000 cc of water) or glycerin enemata (glycerin, 120 cc followed by water 60 cc injected high in the bowel), and if these fail pituitrin 1 cc hypodermically, repeated in a half hour,

may prove efficacious. Elimination of milk from the diet may be necessary as well. When the patient is first seen he should be given a cathartic if none has already been taken and this should be followed the next morning by a saline purgative. After this enemata may be relied on to cleanse the bowel every second day inasmuch as the diet contains very little residue.

Pain is one of the very troublesome symptoms in some cases. It is produced by the pleurisy which accompanies the pneumonitis and is the cause for the rapid and shallow breathing so often seen in the early stages of the disease. Morphine is often required to quiet this pain but it is advisable to use as small a dose as possible on account of the paralyzing action which morphine exerts on the intestinal wall. Enough relief may be gained from $\frac{1}{16}$ or $\frac{1}{12}$ of a grain to enable the patient to fall off to sleep and this dose may with absolute safety be repeated often. Before morphine is resorted to, an ice-bag should be tried and if this is found unavailing a tight chest swathe applied. The non-productive coughing should be stopped by heroin (easily given in lozenges containing heroin, gr. $\frac{1}{12}$).

Delirium must be controlled and if morphine alone fails *Schlesinger's* solution may exert a quieting effect. Occasionally its effect is just the opposite and it serves only to increase the restlessness.

If cyanosis and dyspnea become prominent symptoms great relief may sometimes be had from the administration of oxygen. This is best done in a suitable oxygen chamber but quite satisfactory results can be obtained by bulbing the oxygen through a water jar and into a soft-rubber catheter which has been introduced through the nose to a point where its tip is just visible back of the soft palate. This method is less disturbing to the patient than the funnel and is also more easily performed by the attendant. Fresh, cool air is most comforting to the patient and aids in reducing any restlessness. Exposure should be avoided.

Doctor's orders. Absolute rest (give details).

Force fluids to 3000 cc.

Soapsuds enema every two days if necessary.

Cold sponging if necessary for temperature over 103° F. every three hours without moving patient.

Ice-bag to head or chest for pain.

Chest swathe for pain when needed.

Morphine, gr. $\frac{1}{12}$ (hypodermically) for pain if necessary; repeat in one hour if necessary.

Turpentine stupes if necessary for distention.

Digitan, gr. $1\frac{1}{2}$, every four hours 12 doses.

Specific therapy.	Serum.	Horse (*Cole et al.*)
		Antibody extract (*Huntoon*).
		Chicken (*Kyes*).
		Convalescent human serum (*Stengel*).
	Vaccine.	Prophylactic (*Austin and Cecil*).
		Therapeutic (*Rosenow*).
	Chemical.	Quinine.
		Numoquin (Optochin).
		Alkaline.

Of the eight kinds of specific therapy charted above the Type I pneumococcus serum developed by the Rockefeller Institute workers is the only one that has received enough of a trial to warrant analytical discussion.

Kyes' chicken serum (prepared by further immunizing the already immune chicken to the various types of pneumococcus) has been used in Chicago in the Cook County Hospital and also tried at Camp Grant. The statistics relative to the case mortality are suggestive (a reduction from 45.3 per cent to 20.8 per cent in the Cook County Hospital, and a mortality of 7.7 per cent in 322 treated cases at Camp Grant) but the reactions following its use coupled with other reasons led to modifications and I have seen no further statistics.

An attempt to use therapeutically the immune serum obtained from convalescent pneumonia patients by bleeding them soon after their crisis was made in Philadelphia by *Dr. Stengel* and reported last year. This method is not only attended by great technical difficulties but is also open to many theoretical objections. The chief objection is that serum from convalescent patients is never found to be as rich in specific antibodies as is the serum produced by animal immunization, and treatment with this latter form of serum has already been discarded as useless in all types except Type I. (I allude of course to serum from animals immunized to Types II, III and IV pneumococcus.)

Prophylactic vaccination with killed cultures of Type I, II, III, pneumococcus was performed by *Austin and Cecil* on 12,519 soldiers at Camp Upton. During a comparatively short period of observation the control group showed many more pneumonia cases, and, more upper respiratory infections as well, than did the vaccinated group, and it was noted that what cases did occur were of a very much milder form. We can hardly all of us be vaccinated every November but in suitable cases this form of treatment may be of real service.

Rosenow developed a partially autolyzed vaccine with which he treated cases of pneumonia. Little is known as to the variety of cases treated but his mortality in a group of 200 cases was as low as 7 per

cent. This method has not met with general acceptance and it has not been given a sufficient test so that we must pass it by with a mere mention.

Of the drugs which from time to time have been advocated quinine has recently returned to prominence as a specific in pneumonia. Many years ago it was used very frequently as an antipyretic and therefore often in pneumonia. In 1911, *Morgenroth and Levy* announced the discovery of a quinine salt which they called optochin. In the test tube this drug was found to have an almost unbelievable power to kill the pneumococcus. No very extensive therapeutic tests were made in this country as it was soon learned that occasional toxic manifestations were accompanied by lesions in the optic nerve. In Germany, however, a basic salt has recently been prepared which is said to be harmless and at the same time very efficacious in the treatment of lobar pneumonia. This substance is known as numoquin. It is brought to your attention now because the writer believes that when sufficient knowledge about its use is obtained we shall have a most valuable adjunct to our armamentarium. Until that time however we may if desired, safely turn to quinine which is said by some writers (*Cahn-Bronner*) to surpass optochin. Painful local reactions usually follow the hypodermic injection of quinine so that a high dilution is necessary. One satisfactory preparation which may be obtained at any drug store is:

R.—Quinine muriate 2.0
Urethane 1.0
Aqua dist. .. .. q. s. ad 20.0
Sig.—5 cc intramuscularly—repeat in twenty-four hours and again forty-eight hours later if neccessary.

Alkaline treatment has been advocated by many clinicians but the most thorough study of this phase of the condition (made by *Means*) has demonstrated that not every case suffers from an acidosis. *Means* points out that the production of an alkalosis not only may readily occur but also is quite dangerous. To avoid this it is necessary to make frequent observations on the alveolar air and the blood CO_2. This fact complicates the procedure to such an extent as to make it inapplicable for general routine use.

The form of specific therapy with which the writer has had most experience is Type I antipneumococcus serum. During the War he was stationed for three months at the Rockefeller Institute Hospital and from there sent to Camp Meade to treat the pneumonia cases. The first winter there (1917 to 1918) the writer personally treated 50 cases of Type I pneumonia with serum obtained from Mulford.

Table I. — Type I, lobar pneumonia (Camp Meade)

	Number	Died	Mortality, per cent.
Treated	50	3	6
Untreated	7	0	0
Total	57	3	5.3

It will be noted from Table I that only 3 cases died and it should be added that 1 of these 3 was treated first on the sixth day of the illness having been brought in moribund; 1 had a tuberculous cavity which practically involved the whole left upper lobe, and the third, though operated on by mistake for a suspected empyema before being seen by our service, was apparently cured of the pneumonia only to die ten days later from a meningitis. In the treated group there were no complications other than those mentioned above. There was unfortunately no control group.

Two years later while resident at the Boston City Hospital, the writer supervised the treatment of 75 cases of Type I pneumonia with serum obtained from the Massachusetts Board of Health. The cases comprised men and women of all ages and varieties of physical condition, admitted, many of them, late in the disease. The mortality rate in this group of cases was 17.3 per cent. Of these cases (56 cases) which were treated during the first week of the disease only 7 died, giving a mortality of 12.5 per cent.

During the next two years, under *Dr. E. A. Locke's* direction, every serum treated case was controlled by a similar untreated case. The controls were made to compare clinically as nearly as possible to the treated group. It will be seen from the Table (II) that the mortality in each group was about 17 per cent.

Table II. — Mortality, rate, 145 treated: 71 control cases (Boston City Hospital)

	Number cases	Number deaths	Mortality, per cent.
Group A	75	13	17.3
Group B	70	12	17.1
Totals	145	25	17.2
Control Group B	71	12	16.9

In a recent address delivered before New York Academy of Medicine, *Dr. Locke* carefully analyzed the serum treatment of pneumonia and brought out, among many interesting points, the fact that the average mortality obtained in 6 civilian hospitals in

Boston, New York and Baltimore was 19.3 per cent. From 11 Base Hospitals in the various army camps, however, an average mortality of 9.5 per cent was obtained, and the Rockefeller Institute Hospital figures show 195 cases treated with a mortality of 9.2 per cent. These statistics seem to show that, although serum treatment of Type I lobar pneumonia is of definite value in reducing the case mortality, it is a procedure which requires exceptional facilities and the service of highly trained specialists.

Cecil at the Bellevue Hospital, and *Connor* at the New York Hospital, have for the past few years given a thorough trial to a new form of treatment. This consists of the administration of a polyvalent antibody extract prepared by *Huntoon* of the Mulford Laboratories from horse serum which has been highly immunized against the fixed types of pneumococcus (Types I, II and III). This preparation is a protein-free suspension of specific antibodies in salt solution. The results from treatment with this preparation obtained at the Bellevue Hospital are summarized in Table III.

Dr. Cecil, who has very kindly loaned the writer some of his lantern slides, asks that it be made clear that the intravenous injection of this substance late in the disease is attented by many severe reactions which, in a few instances, have terminated fatally. For this reason subcutaneous injection of larger amounts is now being tried and the results will soon be announced. Both *Dr. Cecil* and *Dr. Connor* feel encouraged to go on with this work on account of the very definite indication of the value of the method. If circumstances are favorable this preparation will soon be available for general use.

Table III. — Comparison of death-rate in treated and control series

Antibody Wards				Control Wards			
Type	Cases	Deaths	Rate, per cent.	Type	Cases	Deaths	Rate, per cent.
Pn. I . .	158	21	13.3	Pn. I . .	162	36	22.2
Pn. II . .	83	23	27.7	Pn. II . .	67	27	40.3
Pn. III . .	73	29	39.7	Pn. III . .	60	24	40.0
Pn. IV . .	110	18	16.4	Pn. IV . .	121	29	24.0
Total	424	91	21.4	Total	410	116	28.3
Strept., etc.	48	24	50.0	Strept., etc.,	35	12	34.3
Unclass .	36	14	38.8	Unclass. .	47	20	42.5
Gr. tot.	508	129	25.3	Gr. tot.	492	148	30.0

Summary. 1. We must never lose sight of the importance of general therapeutic measures in the treatment of lobar pneumonia.

2. Of the special measures Type I antipneumococcus serum is the

only one which has given satisfactory results in a large enough series to warrant its further use.

3. Quinine therapy seems very promising and may subsequently prove to be of great value.

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MODERN APHORISMS FROM THE INTERNAL CLINIC, WRITTEN FOR THE PRACTISING PHYSICIAN

THE IMPORTANT DISEASES WHICH ARE OF DAILY OCCURRENCE

A. F. SOER, ROTTERDAM

PNEUMONIA

INTRAMUSCULAR injections of quinine may have a very favourable effect on lobar pneumonia.

To see a patient playing draughts in the Ward on the fourth day of his pneumonia is striking.

If necessary the injection may be repeated on the following day.

Quinine per os seems to do nothing.

Then it appears rapidly in the blood, but is out again speedily.

Hence a deposit of quinine seems to be better.

Only pneumococcal pneumonias are accessible to this treatment.

The patients are as a rule much more speedly afebrile.

Even an entire arrest of the illness may be observed.

The improvement in the general condition is striking.

The poor patient is saved a great deal of suffering in this way.

All the birth pains of optochine might have been saved.

Few are refractory to quinine.

Quinine is really one of the most powerful of drugs.

One needs only think of malaria, angina, pneumonia, auricular fibrilltation and Ménière's disease.

In addition it is a stomachic, tonic and antipyretic.

Quinine should be injected early in lobar pneumonia.

Furthermore fewer complications seem to occur in this treatment.

(*A. F. Soer.* Moderne aphorismen uit de interne kliniek, geschreven voor den practiseerenden geneesheer. De dagelijks voorkomende belangrijke ziekten. Derde en laatste bundel. Rotterdam, 1924, p. 71)

THE DEVELOPMENT, DURING THE LAST 75 YEARS, OF OUR VIEWS CONCERNING DISEASES OF THE HEART AND CIRCULATION

(DE ONTWIKKELING IN DE LAATSTE 75 JAREN ONZER OPVATTINGEN OMTRENT ZIEKTEN VAN HART EN BLOEDSOMLOOP)

PROF. DR. K. F. WENCKEBACH, VIENNA

IN this lecture given at the festival gathering of the *Nederlandsche Maatschappij tot bevordering der Geneeskunst* (Netherlands Medical Society) at the Hague on the 8th July 1924, regarding quinine as a cardiac agent the author said as follows:

It is already possible now to combine many of the various forms of arrhythmia into groups, which may be ascribed to one and the same cause, only differing in form and constellation. Thus, in this department, which was so much split up into small sections, the broad line of a simple classification again becomes visible.

The practical advantages of this are making themselves manifest. It has now been convincingly shown that irregularities of the rhythm of the heart are really not the sign of a serious disease of the heart, but are functional derangements which may even occur to otherwise sound and strong hearts. Their clinical importance lies in the fact that, owing to their deviating mechanism, they very unpleasantly affect the patient, destroy his feeling of well being and continually disquiet him and fill him with anxiety as a "memento mori"; at the same time they disturb the pumping action of the heart and may even result in considerable derangement of the circulation. Only slowly, with the ripening of our knowledge, have we succeeded in finding new means for eliminating this undesirable symptom.

Digitalis is even now considered as effective, not as a means for strengthening the heart, but as a damper for an over-stimulated heart; and instead of rest physical work is frequently the best means to expel extrasystoles and even conductive disturbances. The "nervina" disappointed us, they are effective at most for a moment. Here again it is the old agents which, with more correct and sharper indication, can be fruitfully applied: strychnine and quinine, which now again cannot be sufficiently praised. The first agent formerly used in

cardiac weakness is now in the ascendant again as a vasomotor agent. Quinine was so much in honour at one time as a cardiac agent that the Viennese clinicist *Oppolzer* reckons it, along with rest and digitalis, as our three most powerful therapeutic means in diseases of the heart.

Stokvis in his text-book points to the fact that quinine, owing to its damping of an excessive digitalis action, may, in many respects, be called an antagonist of digitalis. *Pel* always gave digitalis and quinine together, because he found that this mixture had a better effect on his patients than digitalis alone.

I myself .... refused to give quinine on the strength of scientific considerations, because as a matter of fact, "really and finally" it paralyses the heart. How thoroughly I was in the wrong was shown to me by the following happening: one day a patient came to me, by chance or possibly not by chance, a Dutchman, who told me that he had a means for getting rid of the so intractible perpetual arrhythmia from which he suffered. He furnished proof by appearing before me on the following day with a regular pulse. As I threatened that I would not let him out of my room alive if he did not communicate his "trick" to me, he acknowledged that in such cases he took a gram of quinine. Gone was my supposed scientific argument, but, what a new prospect! Soon quinine was found — though only exceptionally satisfactory in case of complete arrhythmia — to be an unsurpassed agent for the cure of all those irregularities which are due, not to weakness of the heart, but to *excessive* work of the heart, hyperkinesis of the heart, in extrasystole, by injection into the blood in attacks of precipitation, in exophthalmic goitre and in the so obstinate tachycardia in young persons. *W. Frey* showed that quinidine acts more powerfully especially in arrhythmia perpetua than quinine and there are now but few irregularities which we cannot overcome by these means. But at the same time we know that where there is true weakness of the heart, these paralysing agents must be used with the utmost care, as otherwise they do more harm than good. So here again we are back to what had been shown by clinical experience formerly as wholesome and curative, but on a higher plane, with better insight and better results. From this example it will likewise be seen how very much the stupid talk about the progress of science and the stagnation of our knowledge of treatment is beside the truth and how perfectly readily "school medicine" frequently reviled, is willing to abandon unjust ideas and to avail itself of all that it finds to be good.

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THE TREATMENT OF HEMORRHOIDS BY SCLEROSING PERIVENOUS INJECTIONS. HISTOLOGICAL EXAMINATION OF HEMORRHOIDS TREATED BY THESE INJECTIONS

(TRAITEMENT DES HÉMORROÏDES PAR DES INJECTIONS SCLÉROSANTES PÉRIVEINEUSES. EXAMEN HISTOLOGIQUE D'HÉMORROÏDES TRAITÉES PAR CES INJECTIONS)

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THE treatment of hemorrhoids by injections causing sclerosis is not in good repute in France. It was condemned here, several years ago, by first-class surgeons whose influential opinion is law. It is therefore a most difficult task to attempt to fight current setting so strongly. If nevertheless I attempt the task, it is because since these criticisms were directed against the method, its technique has evolved, the processes have been modified, and, on the other hand again, my personal experience — already extending over three years — has proved to me that it would be wrong to forego systematically a treatment which, under certain well-defined conditions, is the right thing in the right place.

I certainly do not intend to draw a parallel between the treatment by injections and the surgical methods; and as far as I am concerned I shall not dissuade a patient from surgical intervention if such is his wish. and if I do not see any counter indication. But it must not be forgotten that, owing to fear or prejudice, some people prefer to remain for years with procident or bleeding hemorrhoids rather than be operated upon; and that others cannot be operated upon for very good medical reasons, (impeded portal circulation, pathological cardiac-arterial system, etc.). In these patients the slow and very progressive withering of the hemorrhoidal masses, the bunches being treated separately at chosen intervals, will not have the very real and sometimes dangerous drawbacks of the sudden suppression of the hemorrhoidal flow; drawbacks sometimes so considerable that hemorrhoids have, in all languages, been given most laudatory names:

veines d'or, vena de oro, goldene Ader, Zoolote, etc.... Finally, when the patients are too debilitated by repeated hemorrhages, neither the operation nor the anesthesia can be performed, but the injection can be made without any delay.

For a long time the only substance employed was carbolic glycerine, which *Mitchell* brought out in America about forty years ago. The opposition which we have pointed out above was called forth especially by this substance. But other medicaments have been injected: ergotine (*Everett*), boiling salt water (*Lofton*), iodoformed ether, (*Beck*), adrenalin (*Krukenberg*), quinine and urea hydrochloride (*Terrel*), 96% alcohol (*Boas*). Out of this long list I shall retain only the three methods most employed:— carbolic glycerine, 96% alcohol, and the double hydrochlorate of quinine and urea.

The technique used for the injections of carbolic glycerine varies very much with the authors; some inject a pure concentrated solution, others a solution very much diluted, down to 12½%; the quantity injected varies from one to twenty drops; some perform the operation in one sitting, others in successive sittings. Some keep the patients in bed, others allow their patients to walk immediately after the injections. This is, how Professor *Roux* of Lausanne, one of the strongest advocates of this treatment, operates: After general anesthesia on most occasions followed by dilatation of the anus, this author injects one or two drops of the concentrated solution in the centre of the hemorrhoidal nodule, and he starts the injection from the skin without ever getting near the mucosa, so as not to produce any sphacelus. The patient must rest for two days after the operation. Since 1890 *Roux* has not performed more than a dozen incised operations for hemorrhoids. He has treated hundreds of cases by injections of carbolic glycerine with complete success, without any serious mishap, and without a relapse when the patient takes the indispensable precautions to avoid injury to the rectum.

I have no personal experience of this kind of treatment, but I happened to examine several patients treated by Professor *Roux* and by one of his pupils, and, generally speaking, the results were very satisfactory. I found a relapse in one of these patients.

Boas proposed, in 1915, to replace the injections of carbolic glycerine by injections of 96% alcohol. This is the technique he recommends:— After having shaved the perianal region and made a local anesthesia with injections of novocain and adrenalin at ½%, he applies for twenty minutes on the anal region, a *Bier* cup, so as to draw the hemorrhoids well out; he then injects in each of the tumours a small quantity of 96% alcohol (never more than ½ to 1 c.c.); all the tumours

are treated in one sitting, and after the operation the hemorrhoids are pushed back into the rectum. If the local anesthesia is good the patient does not usually feel any pain. The whole operation lasts two minutes. After the injections, the patient is put to bed and remains in absolute rest on his back for 24 hours; light diet for 3 or 4 days; bed for 8 days. At that moment it is easy to feel by rectal examination that the hemorrhoids have changed into a hard cord which finally completely disappears in a few weeks.

I tried the injections of 96 % alcohol twice; in each of these cases the final result was excellent, but the patients were in great pain for the first two days.

The process to which I gave the preference consists of injecting a 5 % solution of double hydrochlorate of quinine and urea. I have used it regularly for the last three years and have treated a great number of patients, but I can only use, for my statistics, 52 cases concerning patients whom I was able to follow closely.

These injections are only meant for internal hemorrhoids, which must be found with the anuscope, without any local anesthesia. My technique has changed since I began these injections. At first, I injected a few drops in the hemorrhoids themselves, and then I added sub-mucous injections to the intravenous injections. For the last six months I have adopted the practice of giving these injections solely in the sub-mucous cellular tissue, at the base of the hemorrhoids. This starts a local oedema, and later sclerosis, which hinders the venous circulation. I inject each time 3 to 5 c.c. once a week; 6 to 10 injections are generally necessary to obtain a result. *Aaron* (of Detroit), has just published an article in which he says that he obtained very good results without exceeding 4 submucous injections.

A certain amount of preparation is indispensable; the patient must take an enema three hours before the injection, and introduce, morning and evening, during the period of treatment, a bismuth suppository which adheres to the mucosa, and protects it to a certain extent from the contact of foecal matters; besides, in order to avoid infection, it is necessary to take the greatest aseptic precautions just as if it were a case of actual surgical intervention. The hemorrhoid which is to be treated must be painted with iodine before and after the injection; the instruments and the liquid to be injected must be carefully sterilised. The needle must be as fine as possible — and care must be taken to avoid wetting it with the solution which is to be injected, as it is slightly caustic. The injection must be made *very slowly*.

The injection must be postponed with every patient suffering in

the anal region. The hemorrhoids themselves are not painful; if there is any pain it is due to a fissure[1] or to an inflammatory outbreak which must first be allayed. A preliminary treatment by high frequency is then very useful. Before proceeding with a new injection, it is as well to make sure, by rectal examination, that the preceding injection has not left any painful inflamed nodule.

During the whole period of the treatment, the patient must follow the usual diet of people suffering from hemorrhoids: no wine, no coffee, no mustard, no spices, etc.

The injections do not require either a nursing home or hospital; they constitute a typical consulting surgery treatment, a real ambulatory treatment. The patient who has been injected must simply remain sitting for one hour before resuming his usual work.

In the large majority of cases, the injection is absolutely painless, and this is easily understood as the quinine and urea solution has an analgesic action which lasts several days; the cases in which the injection was painful are few. When there is pain it is at the first injection when the tissues are not yet anesthetized.

Two of my hospital patients had violent pains immediately after their injection; they ceased during the course of the day. Two others have twice had a slight difficulty in urinating. The injection is sometimes followed, the next day or the day after, by a loss of blood. One of my patients who subsequently made a complete recovery, lost more blood during the eight days which followed the injection than before the treatment. Hemorrhage is generally avoided by injecting the liquid very slowly and withdrawing the needle very gently. I had twice painful inflammatory nodules, which occurred at the point of injection: I was once obliged to stop the treatment for eight days, another time for fifteen days. These mishaps never reached a point at which the patient had to stay in bed or required a special treatment: *in no case has it been necessary to abandon the treatment.* Patients have themselves asked for the resumption of the injections; in the hospitals where, as every one knows, it is rather difficult to get the patients to return regularly to the outpatients' department, there is, so to speak, no defection as regards the treatment of hemorrhoids. This can be explained by the relief which is due partly to the action of the medicament on the sensation of heaviness, the pruritus and the ano-rectal discomfort.

Four of my patients who had received 10 injections started again to bleed, six, eight or ten months later; a new series of injections had

1 With M. *André Cain* I obtained a rapid success in treating the anal fissure with injections of quinine and urea. We intend to continue our experiments.

to be given which this time, seems to have produced final results. One wonders whether, in these patients, the first treatment had been sufficiently intense, and if a few hemorrhoids had not been left untreated. But this cannot be said of two patients who suffered from relapses six and eighteen months later. Both had profuse hemorrhages which nothing could stop. One of them who was sent to me by Dr. *Ovide Benoit*, was the sister of a hemophiliac; she had not real hemorrhoidal tumours, but a real sphincterial hemorrhagical rectitis which bled over its whole surface; injections had been the only treatment which mastered these hemorrhages. She had been given 20 injections and had left Paris six months past, completely cured. She has just written me to say that the hemorrhages have started again. The other patient, also treated with great perseverance, remained in good condition for a year and a half, and then suffered again from intense hemorrhages. Despite her aversion to surgical treatment, Dr. *de Martel* operated on her, and I want you to examine the histological slides which come from this operation. The mode of action of the injections is clearly to be seen on the slide; they produced a submucous and perivascular sclerosis which encloses the vessels.

This is the report of the histological examination:

1. In the areas where injections have been recently made, the connective frame which unites the hemorrhoidal dilatations is oedematised, the infiltration of serofluid renders the fibrillar structure of the connective tissue apparent and gives it a hairy aspect. But the veins themselves are not modified; they are not thrombosed, they are not surrounded by any leucocytic infiltration, their endothelium is intact.

2. Where the injections are of old standing, the process of sclerosis is more apparent. The ratio is inverted, the connective tissue is exuberant, while the lumen of the veins is smaller.

Some of the veins have not lost their permeability, and one notices that their walls are intact, their endothelium unmodified, their passage free. But this passage is progressively narrowed. It becomes smaller, sinuous, irregular, and finally it disappears. All that remains to mark the track of the vein is a cellular trail made of endothelium and muscular cells of the vein.

At certain points these cellular trails are very abundant and stand out against the homogeneous appearance of the connective tissue which holds them. This tissue is essentially formed of bunches of collagen extremely poor in cells. A feature of primary importance is the absence of inflammatory reaction and of lympho-plasmatic infiltrates. We have not yet studied in detail the reaction of the elastic tissue

in the course of this provoked sclerosis. It would be very interesting to know what happens to the elastic tissue proper of the hemorrhoidal veins and to what extent the sclerosis is elastigen.

Conclusion:

1. The sclerosis produced is essentially perivenous and it acts by progressive choking and throttling of the hemorrhoidal distensions, and not by thrombosis.

2. The process is aseptic and non-inflammatory. The connective tissue reacts on contact with the injected substance by an excessive secretion of collagen substance. The sclerosis is not the result of a previous multiplication of fixed or migrating cells.

Out of my 52 patients, 6 had relapses of hemorrhages, and 4 had their hemorrhoidal prolapsus hardly modified or not at all. It must not be concluded from this that all the other patients are definitely cured, as some of them received their last injection not more than four months ago. But what can already be asserted is that *without exception all the patients who received injections experienced a real relief.* In order to make it possible to appreciate the results which I obtained with the quinine and urea injections, I must point out that I did not give injections to any and every patient who was suffering from hemorrhoids. Everyone knows that hemorrhoidal outbreaks can be cured by a few days diet and local topica. Every one of the patients I treated had already had recourse to the usual treatments, but without results. They were suffering from hemorrhages, alarming by their abundance or their recurrence or else they had an hemorrhoidal prolapsus or even both, prolapsus and hemorrhages.

The results in cases of prolapsus are sometime especially favourable, and this should not be lost sight of, because if we have means of stopping hemorrhages, we have no palliatives which will treat prolapsus. I may mention as a favourable case, the history of a patient, 71 years old, who was sent to me by Dr. *Felix Ramond.* He suffered from a prolapsus with hemorrhages, the prolapsus protruding at each stool, and which he was obliged to push in again. This prolapsus sometimes came out during a walk. This man whom I treated a year and a half ago, has no more hemorrhages; the prolapsus which is very much reduced, disappears by itself after a stool; the patient told me that he felt a different man after the treatment.

I will also mention the case of a patient of Dr. *Raoult* of Vernon, who had fallen into such a state of post-hemorrhagic anemia that I was called in, about three years ago, to find out if the hemorrhoids

were not accompanied by cancer. I made, on the spot, four injections and since then, the patient has not had any more hemorrhages.

Dr. *Raoult* wrote 29th January 1923: "The alarming hemorrhages for which you were called in have never recurred;" the patient has not had any "smaller" hemorrhages either.

It is naturally difficult to draw a comparison with the other methods of treatment. I do not speak of salves, suppositories or internal medicaments which the patients had all used to a great extent before coming to see me. The results were certainly superior to those of high frequency and of diathermy (which is sometimes painful) for I treated many patients who had not had any relief from electricity. As I mentioned above, I do sometimes give a few electrical applications before I start the injection treatment.

As regards the injections of carbolic glycerine and of alcohol, I am led to believe that they are superior to the injections of quinine and urea when the *Roux* and *Boas* methods are used, but these methods constitute real surgical treatments which necessitate local or general anesthesia, a stay in bed and a severe diet. Better results than those I indicated would perhaps be obtained if the quinine and urea injections were given under the same conditions.

I stated above that the injection methods could not be compared with the surgical methods, which count thousands of cures, but the injections have not the same indications as these methods. In casting up the account of the surgical treatment, it must not be overlooked that in hemorrhoids it is very painful, at least during the 48 hours which follow the operation. Relapses are not exceptional and, worse still, it may happen that the surgical intervention is followed by stricture of the anus, or by incontinence at least partial (liquids and enemas). Like many physicians, I have seen examples of these mishaps, occurring not indeed to young and inexperienced surgeons, but even to our leading surgeons. As Prof. *Quénu* says: "The surgical treatment (of hemorrhoids) entails more difficulties than would be believed at first sight. It is not always simple, it is even often — I do not hesitate to say — more complex than the removal of an ovarian cyst".

Conclusion.

The treatment of hemorroids by injections causing sclerosis is worthy of a place alongside the surgical methods. It has its precise indications, even if more limited than the incisive methods. The final results of the quinine and urea injections are perhaps inferior to those of the carbolic glycerine and 96% alcohol injections, but they have not the same drawbacks. They do not require general anesthesia or local anesthesia.

They do not require absolute rest in bed; they are a typical ambulatory treatment and enable the patient to follow the treatment and at the same time attend to his business. If they do not always radically cure the patient, it can at least be stated that there is always a positive improvement; besides, the method is absolutely painless, and performed by experienced hands, never produces any mishap.

(*Bulletins & Mémoires de la Société Médicale des Hôpitaux,* Paris. Meeting of 11 May 1923, p. 686—693)

THE TREATMENT OF HAEMORRHOIDS BY SUBMUCOUS INJECTIONS OF CHEMICALS

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The chemicals used in injections.

AT St. Mark's Hospital I have experimented with the following chemicals: carbolic acid, quinine and urea, iron perchloride, ergot, lead acetate, alcohol, and formalin. There is no doubt that carbolic acid is the best of all, though quinine and urea gives almost as good results. The latter should be used in 5 and 10 per cent. solutions.

(*British medical Journal*, London, July 19, 1924, p. 100-102)

ACUTE LUMBAGO

SIR, — Those of us who have had personal experience of "the exquisite pain" caused by an attack of acute lumbago ought to be specially grateful to Mr. *H. S. Souttar*, F.R.C.S., for his quinine and urea hydrochloride discovery *(British Medical Journal*, November 17th, 1923, p. 915). As regards the drug itself I have used it for years, but it had not occurred to me to use it as Mr. *Souttar* has done.

As regards the acute attack, I am sure that it is due to the retention in the dorsal fascias and aponeuroses of waste substances, which exercise and other measures would have prevented accumulating. In my personal experience the attack has come on when making some ordinary movement in the process of dressing, or even by a cough. The feeling is as if something had snapped or been torn at a point somewhere about the crest of the ilium, and then the back muscles go into extraordinarily painful and disabling spasm. I doubt this being a "protective fixation": it is more like the explosion of a munitions dump. The pain of the tear, or whatever it is, is quite a tolerable affair; it is the exquisite pain of the muscle spasm, and the ease with which it is induced, which is so disabling. Eleven years ago I had a very severe attack, and as soon as I was able to move I was treated electrically by a friend and colleague. The effect of the treatment was entirely to remove the spasm element, although the pain of the *torn* point remained. My next attack began in the second week of this month. It was comparatively mild to begin with, but a sudden movement induced the snap and the paralysing spasm. I had quinine urea hydrochloride at hand and I got a medical friend to give me an injection which contained 1 gram of the drug in 5 c.cm. Mr. *Souttar* used a 1 per cent. solution, and that is apparently sufficient. This injection was given into the hard mass of contracted muscle, which was tender when touched. In less than an hour the spasm was much relieved, and in quite a short time the tendency to disabling spasm was checked. There remained, however, a second *torn* spot, further out along the iliac crest, which was causing a local spasm, so I had the injection repeated on the following day, and with an equally satisfactory result. I am writing this letter on Sunday, and the injections were given on

Wednesday and Thursday last. I offer Mr. *Souttar* my sincere gratitude. — I am, etc.,

Edinburgh, Dec. 23rd, 1923. WILLIAM RUSSELL

(*British Medical Journal*, London, Jan. 5, 1924, p. 37. Correspondence)

WAR EXPERIENCES WITH INFECTIOUS DISEASES
(KRIEGSERFAHRUNGEN MIT INFEKTIONSKRANKHEITEN)

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INFLUENZA

THE second epidemic of influenza (pandemic) in October 1918, resulted in fewer admissions than the first. Very special stress must be laid on the exceedingly good effect of the quinine treatment (*Blesch*) and on quinine prophylaxis. In no case did I observe serious lung complications, which were otherwise so frequent and so dreaded, if quinine hydrochloride (0.3 gram twice or more frequently per day) was given early. Those who received by way of prophylaxis 0.3 gram of quinine hydrochloride every 2 to 3 days escaped the illness, or had it in a very mild form. I also found this fact confirmed after the war, both in the army and in private practice.

(*Zeitschrift für Hygiene & Infektionskrankheiten,* Berlin, **103:** Part 2, 1924, pp. 241-252)

THE TREATMENT OF EXOPHTHALMIC GOITRE
(OVER DE THERAPIE DER BASEDOW-ZIEKTE)

PROF. DR. F. DAUWE, GHENT, BELGIUM

QUININE, on the other hand, is an invaluable drug, which hardly ever failed me. *Bram* has contrived a quinine test which is based on the fact found by many investigators that sufferers from thyroidism can endure a very large amount of quinine without being troubled by gastric derangements or by cinchonism (tinnitus aurium and giddiness). As regards three-fourths of my cases I can confirm this. With other patients however (few in number) the administration of larger doses of quinine is altogether impossible; the intolerance may even become total. With such patients another remedy must be sought for. With most however the result is brilliant. *Paulesco*[1] reports 42 cases and obtains 42 complete and lasting cures.

The results, according to him, are based on the vaso-constrictor properties of quinine preparations. An angiotonic effect to which there is added a cardio-tonic action. Since quinine and its isomer, quinidine, have been used intensively as a means against arrhythmia we frequently, in cardiac therapy, administer digitalis alternately with quinine; these agents, although to a certain extent antagonistic, mutually strengthen each other.

Although we know but little as to the elementary action of quinine one thing is certain, namely: the retardation of all vital processes.[2] By the absorption of quinine the conversion of glycogen into sugar falls off, and as the albuminous metabolism is also limited with a reduction of the production of urea, it must be supposed that the lowering of temperature which is brought about in patients with increased body heat (fever, exophthalmic goitre) is due mainly to reduction of heat production. Nevertheless it cannot be denied that to a certain extent quinine acts direct on the central heat regulation.[3] In any event it is an agent which has an excellent effect against the chief symptom: accelerated metabolism.

It is now necessary to use large quantities: *Paulesco* gives, in the evening, during the evening meal, *2 to 3* cachets of quinine (hydrobromide, hydrochloride or preferably sulphate) of 0.50 gram each, with

intervals of $^1/_4$ of an hour, thus administering up to 1.50 gram of quinine sulphate. Personally 1 give 0.80 gram in two portions and increase slowly every day. As soon as tinnitus begins the patient must go to bed. For eight days the same agent must be administered, then follow eight days rest, and so forth until clear appearance of results (retardation of pulse, disappearance of exophthalmos and goitre). After this the quinine may be reduced to three days a week until there is complete cure. Short relapses of one or another symptom are combated in the same way.

The duration of the quinine treatment must depend in the first place on the capacity of the patients to tolerate it; the larger the doses tolerated the more speedily the symptoms disappear; in the second place on the time which has expired since the illness began; the more recent the latter the more speedy the cure. Deep-rooted ophthalmic goitre requires a term which will extend over months. Here iodine may assist.

The effect of quinine may also be strengthened by the administration twice a days of 0.50 gram of ergot (secale cornutum).

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(*Vlaamsch Geneeskundig Tijdschrift,* Gent, 1924, No. 19 & 20)

TREATMENT OF BASEDOW'S SYNDROME
(TRAITEMENT DU SYNDRÔME DE BASEDOW)

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THE author, after indicating the various opotherapic treatments, expresses himself as follows with regard to quinine:

The only non-opotherapic treatment possessing any utility in certain well-selected cases, is quinine. Recommended some years ago by *Lancereaux and Paulesco,* among others, it is now beginning to be used by many practitioners in its various forms (sulphate, valerianate, hydro-bromate, phytinate). *Forscheimer,* quoted by *Howard,* advises associating quinine with *ergotin,* and *Watson* advises associating it with *urea* in the form of intrathyroid injections. *We obtained excellent effects from this treatment in young patients having exophthalmic goitre accompanied by great vaso-motor disturbances.* The two conditions last mentioned appear to be very important in determining whether chemical treatment should be undertaken, as has been pointed out by *Freund.* It is interesting to note the power of resistance possessed by patients for this medicine which finally they are able to tolerate in very high doses and for weeks together. We may point out in conclusion, that this class of patients, who derive so much benefit from quinine and withstand it so well, is the class which shows an enormous susceptibility to adrenaline, and this clinical fact concords with the experience of *Clerc and Pezzi* on the pharmacological antagonism of these two elements, quinine and adrenalin.

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ON THE DIURETIC ACTION OF QUININE

(UEBER DIE DIURETISCHE WIRKUNG DES CHININS)

CHIKAYOSHI KATSUBE, TOKYO

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1. *Clinical part.*

IN April 1917 I noticed casually a strong diuresis through quinine in the treatment of a sufferer from amoebic dysentery, who had at the same time shown highly anaemic oedema. I have since then tested the agent in various forms of dropsy, and obtained the following results.

1. The most reliable diuresis is produced in dropsy which is not of renal, cardiac or mechanical nature, particularly in cases of anaemic and cachectic dropsy. Nevertheless it may still appear when the cause has been considerably relieved.

2. The quinine diuresis only lasts as long as the dropsy is present.

3. In healthy or non-oedematous persons it produces no diuresis.

4. The blood pressure shows no alteration.

These clinical observations lead to the view that quinine is to be considered as a histogenetic diuretic as compared with the renal or cardiac diuretics, such as caffein and digitalis, and that its point of attack is to be found in the tissue.

2. *Experimental part.*

On the basis of these clinical observations, I investigated its extrarenal effects as follows.

1. In the first place I observed the relations between quinine diuresis and the alkaline contents of the blood, in order to clear up the question whether the quinine diuresis is based on drainage of the tissue (in the biological sense) or not.

a. The alkaline content of the blood is generally found to have fallen off in dropsy of all kinds.

b. Parallel with the quinine diuresis it gradually increases and declines again when the dropsy reappears.

c. In rabbits which had originally suffered from anacidosis the alkaline contents of the blood are increased by injection of quinine.

d. On the other hand, in animal experiments I found a new phenomenon, so to speak "the pseudoacidosis after dilution", which is not based substantially on the increase of the acid products of metabolism in the body.

Summary.

1. The factors which lead to increase of the alkaline contents of the blood in quinine diuresis are manifold. Consequently it is difficult to attribute quinine diuresis by reason only of this increase of the alkalinity, to drainage of the tissues, although the latter may also be involved in the diuresis. At least however is it to be assumed from these experiments that quinine could promote the mobilisation of the discharges.

2. Whether quinine is able, physico-chemically, to reduce the imbibing capacity of the sol in the tissue, as *Ellinger* recently asserted for all diuretics, I endeavoured to ascertain on his method, but without success.

3. Vascular actions of quinine.

a. With Läwen-Trendelenburg's preparations I proved dilatation of the vessels.

b. The influence of quinine on disposition to oedema or the increased permeability of the vessels was tested on the modified Trendelenburg method, but the result was negative.

4. Animal experiment with quinine diuresis. For this purpose I observed the influence of quinine on the capacity of absorption and excretion of the physiological NaCl solution contained in the abdominal cavity or subcutaneously injected and found that such capacity is very rapidly increased in dogs and rabbits both with administration of quinine per os and also subcutaneously and intravenously.

5. Influence on the formation of lymph.

a. In the normal dog by intravenous quinine injection neither flow of lymph (from the thoracic duct) nor diuresis increased.

b. But in the dog into which the physiological solution of NaCl has been injected into the abdominal cavity, the flow of lymph is clearly increased. In this case the diuresis is increased less than the lymph, the increase being exceedingly slight, particularly on intravenous quinine injection. The dose of quinine used in this case is calculated from the clinical dose (per kilogram 0.002—0.01 per injection) and is very small.

From these facts we have the right to assume that this increase

of the flow of lymph is due directly to the action of quinine and not secondarily to the increased activity of the kidneys.

In the absorption of the ascitic fluid the lymph vessels must play a great part. Therefore quinine must be just as effective in the absorption of the oedemic fluid.

On the other hand it must be an important factor in absorption that the pathological discharges are mobilised, this being in the view of many authors chiefly due to the activity of the cells of the tissue. And in my view quinine promotes the mobilisation of the discharges.

Final considerations.

1. Quinine promotes the mobilisation and absorption of the pathological discharges in as much as the activity of the cells of the tissue, the capillary endothelia of the blood and lymph vessels and the serous endothelia is increased.

2. From clinical and experimental considerations, quinine is to be considered as a histogenetic diuretic which has its point of attack in the so-called pre-renal, tissues in the wider sense.

(Mitteilungen der medizinischen Gesellschaft zu Tokio, 25 Dec. 1924, p. 63—65. Autoreport)

THE TREATMENT OF SCIATICA BY QUININE-UREA INJECTION

ARTHUR E. HERZTLER, M.D., F.A.C.S.
HALSTEAD, KAN., U. S. A.

THE management of this ubiquitous affection has given rise to much discussion which has resulted in many and varied therapeutic measures. I wish to detail a method we have used at this clinic for many years and which, so far as I can determine, has never failed.

Sciatica may be defined as a painful affection of the sciatic nerve. Whether it is a neuralgia or a neuritis is immaterial for this discussion. It has nothing to do, however, with the sacro-iliac articulation, as some orthopedists would have us believe.

The disease begins usually as a dull pain in the lumbar region or sometimes as a typical lumbago but more commonly in the lower gluteal region. Following this premonotory discomfort definite pains extend down the course of the sciatic nerve. The pains may be boring, burning or even lancinating and of extreme intensity. Occasionally the onset is rapid, the initial symptom being sharp, shooting pains extending down the nerve. The pains follow accurately the course of the sciatic nerve. The points of greatest intensity are usually at the sacro-sciatic notch, in the popliteal space and occasionally down the calf in the line of the peroneal and tibial nerves. These points also represent the areas of greatest tenderness. These pains may be continuous but are usually intermittent. They are often worse at night or after exposure to cold. To this clinical picture may be added the classical test of extending the leg on the flexed thigh. The stretching of the nerve by this manipulation increases the pain. This test is less reliable than simple palpation along the course of the nerve. The scoliosis which sometimes accompanies sciatica is indicative only of a severe and long-standing disease and may be ignored in the treatment. When the pain is relieved the spine assumes its normal position.

Though the diagnosis is nearly always easy yet it is possible to make a mistake. Diabetes must always be considered, particularly if

the affection is alternating or bilateral. If there are definite atrophies, paralysis or anesthesias a neurologist should be consulted. In diseases of the hip joint pain may extend down the leg but is usually not so markedly in the line of the sciatic and the points sensitive to pressure are absent. Besides physical examination shows some limitation of movement and the *x*-ray picture will show some bony changes. As a clinical entity sacro-iliac subluxation, particularly, must be banished as visionary, hypothetical and anatomically impossible.

The treatment of sciatica by injections into or about the nerve of normal salt solution, eucaine, tropococaine, stovaine, and many other drugs has been advocated. Vastly more effective is quinine and urea hydrochloride. I have advised its use, both in my book on Local Anesthesia and in volume I of my Case Histories, and I desire here to emphasize its use.

A solution of 1% quinine and urea hydrochloride is used. From 15 to 30 cc. are injected into and about the nerve at the point where it lies over the neck of the femur. This point is selected because when the neck of the femur is reached by the point of the needle the operator knows the needle has been passed deeply enough and that if the nerve has not been located the direction of the needle must be changed.

The technic is as follows: The patient is placed on the unaffected side with the affected thigh half flexed. A point is selected on the line between the tuberosity of the ischium and the great trochanter, somewhat lateral from the midpoint, the exact distance depending on the size of the patient. When the patient stands erect the nerve passes over the edge of the acetabulum, which is a point midway between the bony landmarks just mentioned, (see figure), but when the leg is semi-flexed, as above advised, the nerve glides lateral-ward along the neck of the femur (× in the figure). It is at this point that the needle must strike it.

A wheal is first made in the skin with a fine needle. A larger needle, long enough to reach the depth required (preferably one of 18 gauge, and 4 or 5 inches long) is passed slightly upward as it goes into the depth. If

it strikes the nerve the patient will feel a pain shooting down the leg along the line of his former pains. The operator will perceive a sensation as if the needle had passed from muscle into rubber tubing — a peculiar elastic resistance. If the nerve is not struck the needle will strike the neck of the femur. The operator must then partly withdraw the needle and start in a new direction. Usually he will find that his needle has been passed too far medially. Patient search must be made until the nerve located—by no means always a simple matter particularly in stout patients. The solution to the amount indicated is deposited in this region. In thin subjects I use the lesser amount and in stout patients and for repeated injections the larger amount is used. I usually try to inject 5 cc. of the solution directly into the substance of the nerve and the remainder in its immediate vicinity.

After the injection has been made the patient should be kept in bed a day or two. Recent or mild cases are usually cured by one injection. Severer cases should be reinjected after a week. Severe, long-standing cases, particularly those complicated by scoliosis, may require as many as four or five injections. The intervals between the treatments should be a week or two.

If the injection is made into the nerve a cure is certain. Usually the first injection produces a marked improvement. In rare instances the condition seems to be aggravated but this passes off within a few days. There have been no complications or unpleasant sequellae, and so far as I know there have been no recurrences.

(*American Journal of Surgery*, New York, **38**: N. 4, April 1924, p. 84-85)

THE TREATMENT OF VERTIGO

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AFTER a dissertation on the nature of vertigo, as associated with aural disease, the author continues:

The treatment of vertigo the result of a non-suppurative lesion in the labyrinth demands attention: *a.* during an attack, *b.* between the attack as a preventive measure. During the attack the patient is put to bed with the head slightly raised, hot-water bottles are put to the feet, and calomel, gr.v., administered. As a preventive measure between the attacks the patient should be warned to avoid sudden turning movements of the head, undue exertion, and the watching of quickly passing objects as experienced by looking out of the window whilst travelling in an express train. Sometimes even gazing at moving pictures may incite an attack. Constipation should be prevented, and tobacco and alcohol used only in moderation. The most efficacious drugs are iodides, bromides, strychnine, and quinine. In any particular case it is difficult to say which of these is likely to be most successful, though in those with a neurotic temperament I think bromides are indicated, whilst strychnine is perhaps the most beneficial in debilitated individuals. On the whole, however, I believe that quinine in small doses with or without bromides will be found to be the most valuable drug in warding off attacks of vertigo of this class. A useful prescription is:

R. Quinine sulph. . . . . gr. ½
Ac. hydrobrom. dil. . . . . min. 15
Tinct. aurantii . . . . . min. 20
Aq. ad. . . . . oz. ½
oz. ½ night and morning.

In vertigo unassociated with aural disease the author says that in some cases of vertigo combined with migraine considerable benefit may be derived by taking pil. quininae, gr.l., twice a day, combined with a diet restricted in animal food and strict instructions to the patient to eat sparingly.

(*The Lancet*, London, Dec. 6, 1924, p. 1191)

THE TREATMENT OF VARICOSE VEINS
(DIE BEHANDLUNG DER KRAMPFADERN)

PROF. HENRI BARDY, HELSINGFORS
Chief of the Surgical Department of the municipal Maria-Hospital

PATIENTS who resort to the surgeon on account of varicose veins or complications caused by the latter have, as a rule exhausted conservative methods of treatment such as ideal bandages, rubber stockings, Varikosan bandages and the like. These measures are not really curative treatment in the proper sense of the word but have for their object rather to retard development of the ailment and prevent the occurrence of complications, so that I will confine myself merely to mentioning them.

I would like to divide the true curative methods into 3 groups, namely:

1. Those methods the object of which is to relieve the veins of the pressure exerted upon them by the blood column. This group comprises: ligatures and sections of the V. Saphena magna, and also the cutting away of all subcutaneous veins on the leg on the method of *Mariani and Rindfleisch*.

2. Methods which aim at curing the disease radically by extirpation of the enlarged bundles of veins; either by one long or by several short cuts.

3. Methods seeking to achieve the same result by producing thrombosis of the veins. The thrombosis may be produced either by local injections or by filling the entire enlarged vein system with the liquid which is to bring about the thrombosis.

Which of these methods is to be used in any particular case results first and foremost from the nature of that case but also in part from the preference of the surgeon for one method or the other. Moreover the various methods may be happily combined with each other. In the Maria Hospital at Helsingfors, 288 patients were treated for varices or complications. In 133 cases an operation was made. In these cases all the above mentioned methods except *Rindfleisch's* spiral cut were applied. Where varicose veins had collected in clearly defined aggregations and belonged to the area of the great saphenous

vein, the method selected consisted in extraction of the said veins on *Babcock's* method and in cutting out the enlarged veins. *Babcock's* method is as follows: the great saphenous vein is exposed at the point where it ends in the femoral vein after which it is ligatured as close to the junction as possible and opened. Through this opening a flexible metal sound is inserted in the peripheral part of the vein, the said sound being at one end fiitted with a large ball and at the other with a small ball. If this special instrument is wanting, then an oesophagus sound may be used, as was done by me, to one end of which the small ball, and to the other the large one, is screwed. With the small ball in front the sound is pushed inside the vein like a catheter in the urethra, and as a rule it is possible to push in the sound so far that it can be seen and felt in a subcutaneous vein in the lower part of the leg. This vein is exposed by a cut, and is peripherally ligatured, after which the sound is knocked through the wall of the vein and drawn out of the wound. The large ball at the other end then brings the V. saphena along with it so that it is entirely pulled out. Many surgeons condemn this method because they are afraid for theoretical reasons, that the torn-away branches of veins may cause severe haemorrhage. Practice shows however that this is not the case because the veins extend very much, before they tear, and when they do tear they recede so far into the tissue that they do not bleed. The method is perfectly safe, saves a great deal of time and yields cosmetically beautiful results, for which reason I can warmly recommand it.

In cases where the varicose veins were scattered and practically impossible to extirpate together, we formerly, after extracting the saphena, cut away all the cutaneous veins by a circular cut at the level of the tubercle of the tibia. (*Mariani's* method as described by *R. C. Öhman* in *Finska Läkaresällsk. Handl.* 1913). Last year in similar cases we used injections producing thrombosis, with a solution of quinine (quinine hydrochlor. 4.0 — urethan 2, aqua dest. 30.0). This method, which I will deal with later, was employed by a French doctor, *Génévrier*.

In cases where varicose veins are complicated with leg wounds or thrombophlebitis the treatment was stopped until the inflammation had been removed by rest in bed and application of compresses. In phlebitis we mostly used lead lotion, and for wounds boracic lotion or physiological solutions of common salt together with hot water dressings. In individual cases "*Fischer's* fluid" rendered good service.

Equipped in this way it might be supposed that we were fully armed for the treatment of varicose veins, but unfortunately this is not the case. I have so far not dealt with an incalculable danger which threat-

ens after every operation on large bunches of veins, namely thrombosis and embolism. Let me give an example of this. A young woman in flourishing health called upon me last spring for the treatment of large well-defined and uncomplicated varicose veins. The case was exceedingly well adapted for a *Babcock* operation plus extirpation. On my proposal that she should undergo an operation, she replied that she had hesitated for a long time because she had lost her best friend owing to a blood clot after the same operation. I reassured her by saying that strict rest in bed after the operation disposes of this danger. The operation was carried out and healing completed quite aseptically. When the patient on the 15th day after the operation got out of bed, she fell down dead. The post mortem showed that a part of the thrombus which had formed in the end of the great saphenous, had broken away and had been dashed into the pulmonary artery.

Among the 133 operations which were carried out in the Maria Hospital we observed an other case of thrombosis and embolism. This was a woman of 56 who had been subjected to an operation on the *Mariani* method for a varicose wound in the leg. Fever in the post-operational period was absent, but on the 4th day after the operation phlebitis occurred in the hollow of the knee. On the 7th day abdominal pains were recorded and on the 10th day gangrene in the foot which had to be amputated later. Later on there also appeared embolism in the mesenterial vessels and in both arms, all of which resulted in the death of the patient, which occurred 30 days after the first operation. I would like to add that all larger series of these operations are attended by equally striking misfortune. Thus *B. G. Noble* reports that in 176 sections of the V. saphena there occurred one case ol pulmonary embolism with fatal result. Other statistics, by *Jeannel*, indicate that in 1,444 varix extirpations there occurred 20 aseptic and 2 suppurating thrombi, 3 cases of embolism of the lung and 4 of pyemia. In view of such incalculable catastrophies one is compelled to look around for less dangerous methods of treatment. Even if the saphena is ligatured close to the femoral and the patient allowed to remain in bed for 4 weeks, one cannot be quite sure of him. With entirely aseptic thrombosis the clot of blood hardly causes an irritation of the endothelium of the vessel. In one of my cases the thrombus was not even organised two weeks after the operation. In the other case almost the entire aorta and the right coronary artery was filled with thrombotic mass which was quite loose.

The only manner of precluding the danger of embolism is to create stratified solid thrombi which adhere firmly and in good time to the

wall of the vein. In the Maria Hospital investigations in this direction were carried out by my assistant *Dr. Ulfves*. They related in the first place to the thrombi which form after quinine injections on the method of *Génévrier (Monde Médical* 1922, No. 611). These injections are exceedingly simple to make. The patient sits on the edge of the bed with legs hanging down and the doctor takes his place opposite the patient. After an application of iodine the injection is made with an ordinary morphia syringe provided with a fine point. After making sure by exerting gentle suction, that the needle is in the interior of the vein one-quarter to one-half c.c. of the solution is injected. If a little of the solution makes its way into the wall of the vein or the part surrounding it, this is not otherwise than beneficial. This should be aimed at in particular if the varicose veins are large. The puncture is then closed up with cotton wool steeped in collodium. About 8 cm. higher a fresh injection is made, etc. *Génévrier* seldom exceeds a dose of 4 c.c. at one sitting. At the points of injection thrombosis takes place which may be rather painful in the first days. A week later the method can if necessary be renewed.

With this method of treatment the question, of course, arises whether these thrombi are not just as dangerous as those which form after a ligature of the veins. The great road through the saphenous is open wide. It seems to me that theoretical doubts in this respect must yield to practical experience. *Génévrier* states that the intravenous injections of quinine are innumerable and that he himself has carried out 4,000 of them without embolic consequences. In the Maria Hospital 26 patients underwent this treatment and more than 500 injections were carried out without any accident.

Dr. Ulfves's investigations concerning the action of quinine on the blood are still in progress, but I would like to touch on them very briefly. If a drop of quinine is added to a drop of blood, surprising to say there is no coagulation at all. A microscopic examination shows that the roll formation is stopped. — If the time of coagulation is determined before and after the injection of quinine, it is found that it is reduced 2—2½ minutes, i.e. 25—30 %. By way of comparison I would mention that none of the many agents which promote coagulation and were tried by *Dr. Elving* in the Maria Hospital in another connection possessed so powerful a coagulative property although they were used in heavy doses. Furthermore in dissections of quinine-thrombi it is found that they adhere strongly to the walls of the vessels which are permeated by a bloody gelatinous mass. It appears therefore that quinine exerts a general action on the coagul-

ation process and a local action on the walls of the vessels, e.i. is particularly suitable for creating rapid, firm and safely-adhering thrombi. These facts must as stated be confirmed by further investigations.

By way of completion I would further mention that we used in 2 cases the method of, after the ligature of the saphenous vein, to fill the entire superficial varicose system of veins with a solution of iodine, in this case *Pregl's* solution. The result must be described as splendid. The drawbacks of the method are: *Pregl's* solution is patented and practically impossible to obtain and above all the ligature of the saphenous entails the usual risk of embolism which is incalculable. Possibly the thrombosis of the veins might first be produced by quinine injection and some time later the vascular system filled with *Pregl's* solution.

The surgical treatment of varices leaves behind excellent functional results although small, often harmless, relapses are not infrequent. It is nevertheless our duty to investigate further and above all to attempt to obviate the incalculable danger of embolism. If we should further succeed in curing the ailment without operation and without lengthy stay in the hospital, this too would be a great advance.

Summary.

The writer emphasizes that the operative therapy of varicose veins yields good results, buth that the danger of embolism is an incalculable factor which has hitherto proved impossible to eliminate. At the Maria Hospital, Helsingfors, a series of patients have been treated with intravenous injections of quinine. Investigations have proved that this substance has a two-fold effect, in so far that it reduces the time of coagulation of the blood to a much greater extent than any other known substance and, further, irritates the wall of the vein so strongly as to produce thrombi that become firmly attached to the wall of the vessel.

(*Acta Chirurgica Scandinavica*, Stockholm, **58:** 1924, p. 74—80)

THE TREATMENT OF VARICOSE VEINS BY INTRAVARICOSE INJECTIONS OF QUININE

(LE TRAITEMENT DES VARICES PAR LES INJECTIONS INTRAVARIQUEUSES DE QUININE)

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Comité Médical des Bouches-du-Rhône

THE treatment of varicose veins by local intravenous injections, a question which was received by *Sicard*, who, in 1920, injected a solution of carbonate of sodium, has been of late the subject of several communications regarding new therapeutic agents.

Doctor *Génévrier*, in October last, advised the use of neutral hydrochloride of quinine, while *Montpellier and Lacroix*, of Algiers, extolled bi-iodide of mercury.

Finally, last November, *Sicard, Paraf and Lermoyez* at the Medical Congress, eulogised sodium salicylate.

We thought it of interest to form an independent opinion on the value of each of these drugs, and we propose to give a series of case observations for each of them successively.

We began with quinine hydrochloride, with six cases under observation at the present time.

All our patients had varicose veins with complications: eczema or ulcers.

We treated them with local intravenous injections of the solution of neutral hydrochlorate of quinine recommended by *Génévrier*.

Neutral hydrochlorate of quinine	0.40
Urethan	0.20
Distilled water	3 c.c.

We have to thank Prof. *Reynès* for allowing us to take some observations in his hospital wards, and also Prof. *Gaujoux* and Doctor *Vigne*, who were kind enough to entrust some of their patients to us.

Case I.

S... Giusseppe, 65 years old, entered the Hospital de la Conception on December 8th for treatment of varicose ulcers of the right leg.

He had been suffering from varicose veins for at least 10 years, and had already had several ulcers on both legs. *On his admission* he was seen to have two ulcers, one the size of a two shilling piece on the right inner malleolus, the other, the size of a dollar, on the inner of the same leg. Up to the 16th of December, the wounds were dressed with gomenol oil, and with strips of Vigo plaster.

The limb was placed in an elevated position, but the patient, rather feeble minded, did not remain in that position.

The ulcers, up to that date, cleansed slowly and were always suppurating.

On the 16th December, we injected the quinine solution along the tract of the right internal saphenous vein, first at its origin, on the dorsum of the foot, then higher up, encircling the ulcers, finally every three inches to the middle third of the right thigh.

The dose of quinine hydrochloride was of 400 milligrams.

The patient did not show any pain. There were no local disturbances, no general reaction. The next day, however, there was a slight tenderness to pressure at the points of injection. The ulcers had been dressed on the same day as the injections with strips of Vigo plaster. The patient rested in bed. Two days later, on the 18th of December, the ulcers were found *healed*. The varicose veins on the treated side were, in the upright position, less voluminous than those of the other side.

The patient left the hospital immediately, without waiting for a second series of injections.

Case II.

G..... Charles, 49 years old, cook, entered the hospital on the 16th of December, for rupture of varicose veins in the left calf. Has suffered from varicose veins since 1900, and has already had ulcers.

On his admission, we noticed on the left calf, on its inner side, an ulcer the surface of which was pimpled, and which bled. Enormous winding varicose veins covered the inner side of the left lower extremity. The hemorrhage was stopped with a slightly compressive dressing.

On the 18th of December we made an intravenous injection of quinine. Every three or four inches we injected 1/4 to 1/2 c.c. of our solution into the dilated parts, from the dorsum of the foot to 10 centimetres from the end of the saphenous vein.

In the thigh, the veinous tissue, very distended caused, when the needle was taken out, a slight flow of blood into the subcutaneous tissue.

The next day, December 19th, slightly painfal ecchymosis was observable on the tract of the saphenous vein, at the points of injection.

The ulcer was dressed with Vigo plaster. On the 26th of December it became necessary to renew 4 injections in parts which were still dilated; this time, we only injected about 250 milligrams of quinine hydrochloride.

On the 6th of January, the ulcer is healed.

On the 13th of January however we reinjected into two dilated segments of the saphenous vein, and we considered the patient cured on the 16th of January, with indurated segments on the tract of the saphenous vein, corresponding to as many ligatures which prevent the vein from filling up when changing from the recumbent to the upright position.

Case III.

D..... Antoine, cook, 42 years old, entered the hospital on December 15th with varicose ulcer of the inferior third of the left leg.

The patient had suffered from varicose veins since his 15th year. He successively had trouble in walking, sciatic neuralgia, oedema of the left leg and finally varicose ulcers.

Examination showed an abnormal tract of the dilated inner saphenous vein, which followed the outer side of the whole lower limb. There was an ulceration with hard rims with a pimpled and sanious surface, on the lower third of the left leg, the skin of which was glossy and erythematous.

On the 19th of December a total of 40 centigrams of quinine hydrochloride was injected at seven points on the tract of the varicose veins.

The injection was not painful, and the patient was not at all disturbed. There was a slight flow of blood in three places forming a hematoma. The next day, no reaction except pain under pressure. On the 27th of December, the quinine injection was repeated at three spots which were still dilated.

On the 30th of December, the varicose ulcer had healed, when the dressing was taken off and the patient asked for his discharge.

The saphenous vein showed indurated segments near the injected points, each about 3 centimetres long, which prevented the reappearance of the *Trendelenburg* sign noticed at the beginning.

Case IV.

C... Joseph. docker, 60 years old, attended the Dermatological

out-patients' department on January 17th, suffering from a varicose eczema of the whole left leg, and having an ulcer the size of a half-penny on the inner side of the same leg.

He had been suffering from varicose veins for 10 years and had a varicose ulcer for 2 months in 1921.

The examination showed, besides the eczema and ulcer, a bunch of very prominent varicose veins on the postero-internal side of the left knee, in the upright position.

On the same day, January 17th, 40 centigrams of quinine were injected into the varicose veins. Two injections were, in particular, made into the venous bunch of the knee.

Dressing with gomenol oil. On leaving, he complained only of some heaviness in the leg.

On January 26th, nine days later, though he had not interrupted his work at the dock, the ulcer had healed. The veins were hard at the points of injection, and the varicose bunch of the inner posterior side of the knee formed an indurated area in which no fluctuation was apparant. We injected again, at four points, 1/4 c.c. of the quinine solution and prescribed an ichthyol ointment for the eczema.

Case V.

Miss B..., 31 years old, attended as an out-patient on the 14th September 1922, for skin trouble of the *left leg*. It had started 6 months before with violent itching, which the patient persistently treated with Alibour solution.

The examination showed two areas of oozing eczema. The skin around the edges was brownish, thin and tight. There was an oedema of the leg.

Large bunches of protruding varicose veins were noticeable on the inner side of the left knee and of the thigh, right up to the end of the saphenous vein.

Treatment of the eczema was started that very day with a series of pastes with progressive doses of ichthyol. On October 10th it was much better. But the leg remained oedematous and the varicose veins were still prominent.

Then 3 c.c. of a quinine solution were injected. This quantity was injected at eight different points in the varicose bunch of the knee and along the tract of the saphenous vein.

There was no flow of blood, no pain, and the patient returned home without any difficulty.

On October 14th, the patient stated that her leg was slightly painful and "heavy". The veins were hard. The bunch near the

knee had changed into a hard cake, slightly painful to pressure. The skin covering was unaltered.

On October 26th, the eczema had healed, but there remained a slight brown pigmentation.

The oedema of the leg had decreased. Hard cord with hardly any surface could be felt running along the line of the injected veins, but was free from pain.

The patient did not complain of any trouble.

Case VI.

R... Jules, 39 years old, was examined on the 4th of November last. He showed on both legs characteristic erythematous blotches of varicose eczema.

The left leg showed, in addition, a rather deep ulceration.

The two legs, slightly oedematous, were covered with varicose veins which gathered into one, the internal saphenous, which was very dilated in parts, forming a string of varicose tumours.

We injected half a c.c. of quinine solution in each dilated portion of the string in the left lower limb which we this time treated alone.

The patient felt neither cramp nor pain during the injection.

We prescribed for the dressing of the ulcer of this leg, compresses with isotonic serum, and ektogan powder. We intentionally did not prescribe any active dressing.

On November 12th, the patient complained only that his leg was "like lead". The varicose dilatations were changed in the left limb — the one treated — into a cord, hard, and slightly painful to pressure.

The ulceration had a better aspect, and had granulated. We touched the bottom with silver nitrate. The right leg was then treated with six injections of half a c.c. of solution.

On November 20th, the left leg was no longer painful. The right leg, more recently treated, was still "heavy."

On December 4th, the varicose ulcer had healed, and the eczema was healing. The veins were indurated on both legs at the points of injection.

We may notice that with this patient it was difficult to feel the fluctuations in the varicose dilatations two minutes after the injection of quinine.

And on the other hand, that the patient, a commercial traveller, never interrupted the walking and travelling which his profession necessitated.

These six cases show that the injection of a solution of neutral

hydrochlorate of quinine as recommended by *Génévrier*, can produce the induration of varicose veins, without any appreciable pain to the patients, without crust, and without cessation of their daily occupation. The only thing they sometimes felt was a slight heaviness of the limb.

How do these injections work?

We cannot as yet clearly explain this. *Génévrier* calls them "coagulating injections", and we intend to find out by experiments on animals and *in vitro*, the action of neutral hydrochlorate of quinine on the walls of the veins and on the blood.

We permit ourselves for the moment to compare the effect on sufficiently treated veins to that of repeated ligatures, and we think we may say that they modify the blood circulation of the varicose limbs favourably enough to be a valuable adjunct to the local treatment of ulcers.

M. *Tribet* enquired whether, after the quinine treatment, the varicose veins did not regain their suppleness.

M. *Mathieu* stated that *Génévrier* had seen definitive cures dating from 1919.

M. *Vigne* thought that, clearly, quinine was not the only salt capable of curing varicose veins. He used sodium carbonate, and the vein, far from regaining its suppleness, was as hard as a pen-holder. But the quinine injections were easier to make than the carbonate injections.

M. *de Vernéjoul*, after pointing out that surgery had also given brilliant results, either by saphenectomy or by the operation of *Moresqui*, said that, unfortunately, relapses were very frequent.

M. *Mathieu's* observations were liable to one great objection, namely: that they were too recent. In a varicose ulcer the cause was not a circulatory one only, and he feared a relapse in all these cases.

M. *Roger* dealt with the history of intravaricose injections, and gave the history of the first observation, which induced *Sicard* to treat varicose veins by sodium carbonate. *Sicard* had really beautiful results. However, sodium carbonate is liable to crust formation and he feared that quinine would do the same thing.

M. *Mathieu* had never had any crusts, which might be due to the concentration of the solution employed.

(*Marseille-Médical*, 15 Mai 1923, **60**: No. 10, pp. 550-555)

LOCAL ANESTHESIA BY QUININ SALTS AND THE COMMITTEE REPORT

To the Editor:

A Communication by me with this title was published in *The Journal*, Sept. 18, 1920, and the September, 1920, *Laryngoscope*, in which I gave my experience with the quinin salts, and expressed the opinion that the committee of the Section on Laryngology, Otology and Rhinology on local anesthetics had not quite done justice to quinin as a local anesthetic. I had lately used quinin hydrochlorid, 1 grain in 2 drams of distilled water, with entire satisfaction. Shortly afterward, a patient had a slight slough of the wound, and I reduced the strength of solution to $^3/_4$ grain in 2 drams, since which time I have had no case of sloughing, and the anesthesia has been satisfactory. I then began the practice of using this strength of quinin hydrochlorid for the right tonsil and 0.2 per cent. of cocain for the left (5 c.c.) to secure comparative results. In all cases either 20 per cent. cocain or cocain mud was first applied to each tonsil, but in small amount. In each one of the few cases I have been privileged to operate, the patient has expressed himself as better satisfied with the operation of the right than of the left. The healing after quinin has been at least as good as after cocain, and, the first twenty-four hours, freer from pain.

A little more time (ten or fifteen minutes) is required for anesthesia, and it is well to incise the mucous membrane under the anesthesia from the cocain application and before edema has followed the injection of the quinin.

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(*Journal of the American Medical Association*, Chicago, **83:** July 28, 1923, p. 321. Correspondence)

ON THE UTILITY OF QUININE TREATMENT FOR CANCER

(SOBRE LA UTILIDAD DEL TRATAMIENTO QUINÍNICO DEL CÁNCER)

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MANY years have passed since the days when the treatment of cancer by quinine salts was in vogue. *Jaboulay* held that the cause of this fatal disease was a protozoal parasite, very similar to the *plasmodium malariae,* and as a logical consequence, he thought that quinine would likewise have a special action on this parasite; he therefore advocated its use and the first results were promising. The patients improved, their suffering decreased and life was lengthened.

Yet it was not long before the drawbacks and inefficacy of this therapy made themselves felt. *Jaboulay* advised the use of intramuscular injections containing 0,50 gram of bihydrochlorate of quinine per cubic centimetre, and this method gave rise to various local troubles which are perfectly well known to those who have had occasion to treat malaria sufferers.

In the first place the injections are exceedingly painful, so painful that some patients cannot stand them.

In addition, nodules are formed at the point of the injection, lasting a long time and being also painful.

Finally, the formation of abscesses and eschars refractory to cicatrisation has been observed.

It was however not these local mishaps which contributed most to the relegation of the treatment to oblivion. The magnitude of the evil to be combated was such that they would have been considered as slight drawbacks.

The reason of the abandonment lay in the disappointment which was not long in making itself felt in the persons who had originally devoted themselves with ardour to applying the supposed panacea.

They very speedily arrived at the conclusion that the patients died

just the same though, it must be acknowledged, after having experienced relief of their pains and prolongation of life.

These latter facts were in themselves a success and well deserve to be taken into account. Thus it is that *A. Robin* in his *Treaty of Therapeutics* recommends quinine, which, in his view is the only useful treatment; *Ravet* (of Lyons) in his thesis considers a number of cases of uterine cancer improved by the same agent, and *Castaigne*, in 1912, declared himself in favour of its application in all cases of cancer.

The last mentioned writer endeavoured to avoid local troubles which occurred after the injection, by using a highly diluted solution of bihydrochlorate of quinine (10 %), of which he injected 20 to 30 cubic centimetres every other day, giving on alternate days 1 gram of the same salt per os, in two cachets of 0.50 gram. He was an enthusiastic advocate of the method, not pretending to cure, but to relieve the unfortunate sufferers.

Being familiar with the material which I have just set out in brief, I have myself employed this treatment for years, adopting the technique indicated by *Castaigne*. I have had both good and bad results and have been able to conclude that this therapy has its particular indications and is not useful in all cases.

Needless to say it has not occurred to me to think or to speak of cures in this connection. Yet I hold that in cases like these we must bear in mind the aphorism: *"If we cannot cure let us attempt to relieve"*, adding *"without injury"*.

From my observations I have deduced that *quinine treatment is useful in the painful forms of cancer*, whatever its localisation. It soothes the pain admirably and obviates the use of morphia; this is the secret of its success and of the improvements which, at the outset, were recorded in consequence of its use.

It is well known that the pain of cancer is due principally to the occurrence of a process of cancerous neuritis. The pain exhausts the patients, deprives them of sleep, makes it difficult for them to be suitably fed, and finally produces in them a condition of decline, which is added to the condition due to the actual tumour. It follows logically that if this pain is got rid of or relieved, the patient will experience a sensation of wellbeing and will, by means of restorative rest and sufficient nutrition, regain much of his lost strength.

If, in order to secure this result, recourse is had to morphia, failure will be inevitable because, though the pain is allayed, this is effected by producing a state of intellectual and physical torpor, which is anything but conducive to restoration of strength. Added to this

there is the toxic action of the medicament and the necessity of progressively increasing the dose, if the analgesic action is to be maintained.

I do not believe in the tonic effect which it has been sought to attribute to morphia in these cases.

Quinine, on the other hand, possesses an obvious analgesic action in this as in all forms of neuritis and neuralgia, to which analgesic action there is added its tonic effect and the persistence of these effects.

I will set out in brief form a few cases confirming my statements.

First case.

In the year 1917 I was called in to attend Miss M. C., 52 years of age, Argentine, suffering with chronic aortitis with insufficiency of the sigmoid valves *(Hodgson)* and who was moreover diabetic. I applied suitable treatment for her aortic ailment and ascertained that her diabetes was simple, without denutrition. I omit all that relates to these ailments in order to dwell at somewhat fuller length on the points relating to the subject under discussion.

This lady had furthermore suffering from frequent metrorrhagia, which had occurred after the critical age (menopause). On being examined by a distinguished gynecologist, uterine fibroma was diagnosed and radiotherapy advised. As no practical result whatever was obtained by this treatment and I was attending her, she, by my advice, consulted Professor *Bottaro* who thought that a fungous metritis was in question, though not discarding the possibility of an endo-uterine neoplasm.

He advised surgical intervention (curettage) with further proposed treatment, even going so far as hysterectomy.

The aortic lesion and the diabetes from which the patient was suffering contra-indicated this latter operation, but I was in agreement with curettage being carried out. The anesthesia was produced with ethyl-chloride after alcalinisation of the patient, when she had been put on a fasting diet for some days to bring about dissappearance of glucose. Curettage resulted straightway in the extraction of fragments of tumour which, on examination by Professor *Roffo*, were found to be a cylindric epithelioma.

The post-operative consequences were of short duration and the patient continued relatively well for some time. It was not long however before the abundant and characteristic fetid flow reappeared, while at the same time pains were felt left of the median line immediately above the pubic arch.

These pains became so intense that the patient was continually

shrieking and all the analgesics given per os failed (analgesine, aspirin, phenacetin, guaranin, etc.).

Then I resolved to have recourse to treatment with quinine in the form advocated by *Castaigne* and which I have explained above. The favourable result was not long in showing itself; the patient experienced great relief of the pain after two injections, that is to say, after 4 days of treatment, and the pain disappeared completely shortly afterwards. She was subjected to the action of quinine for twenty days; then I suspended the treatment.

The patient continued well and recovered strength and courage in spite of the fact that the tumour continued to progress and was already palpable in the hypogastrium.

The improvement lasted for two months, at the end of which the pain reappeared just as intense as previously. The patient asked for quinine, the action of which she knew by experience. Fresh treatment and fresh improvement.

Thus this patient continued without suffering to any greater extent, thanks to this treatment, which I administered from time to time and notwithstanding the progress of the tumour which, emerging from the limits of the uterus, extended to the entire abdomen, producing a peritoneal carcinoma with hemorrhagic ascitis which I had to lance on several occasions.

Death occurred in February 1920, about two years after the neoplasm had been discovered and without the acute pains due to neuritis having recurred.

Second case.

Mrs. M. de C., 56 years of age, had been operated in January 1919 for a cancer of the left breast. She passed a period of about six months very well, at the end of which she began to feel intense pains in the arm and neck on the operated side, which reduced her to a condition of positive madness day and night. An examination of the operative cicatrix and the axillary region showed no neoplasmic nodules or ganglionic infarct. The vertebral column was free from pain and possessed good mobility.

I diagnosed cancerous neuritis and advised quinine treatment.

On its application all pains disappeared completely, giving the patient a sensation of perfect wellbeing.

Third case.

This case proves that quinine only improves cancer sufferers by its allaying of pain.

A female patient who occupied bed No. 5 of ward V of the Clinical Hospital, service of Professor *Güemes*, had a cancer of the great curve of the stomach towards the pilorus, Anorexia was absolute. General condition one of entire decline, with occasional vomiting. Quinine treatment produced no improvement; the patient got worse every day in spite of the quinine.

In my practice I have had many other cases to which I have applied this treatment with the relative success which it is feasible to expect from it. I have selected the foregoing from among them merely as a clinical proof of what I advise.

(*La Semana Médica*, Buenos Aires, **31**: No. 5, 31 Jan. 1924, p. 187—189)

CONTRIBUTION TO THE STUDY OF QUININE ABSCESSES

(CONTRIBUTION À L'ÉTUDE DES ABCÈS QUINIQUES)

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HIS study has brought the author to the following conclusions:

1. Quinine abscesses are a frequent and sometimes grave complication of intramuscular injections of concentrated solution of quinine;

2. In the great majority of cases, these abscesses are consequent upon a septic inoculation at the time of injection;

3. Intramuscular injections appear to expose the patients more particularly to abscesses, as they require a very minute technique.

Furthermore when the abscess does occur it is deep, and necessitates lengthy confinement of the patient to bed and sometimes a more or less serious intervention. Finally, it occasionally leaves behind grave sequelae;

4. The method to be selected is that of hypodermic injections of dilute solutions; these ensure rapid absorption of the drug, are painless and harmless or, at the very most, give rise to troubles of a perfectly mild form. Requiring very simple manipulatory methods; they may, with all safety, be entrusted to an assistant.

(Inaugural thesis, Algiers, 1923, p. 51)

PRINCIPLES FOR THE TREATMENT OF FEBRILE ABORTION

(GRUNDSÄTZE FÜR DIE BEHANDLUNG DES FIEBERHAFTEN ABORTS)

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THE author advocates an expecting attitude in the treatment of this ailment and emphasizes that permanent defervescence speedily occurs with the ovum or the remainder of the ovum in the uterus, mostly during the first two days. Very rarely after the fifth day.

The danger of haemorrhage owing to expecting treatment is not considerable. Among 276 cases there were only 27 instances of haemorrhage which compelled an interruption of the waiting treatment, i.e. 10 %, and only a single case of death from haemorrhage.

He further writes:

The most important observation however with which the waiting treatment has provided us is that blighted ova or their remainders may be even spontaneously expelled. As regards this, in the first place, I can report from the material of my clinic, that out of 276 cases treated on a waiting basis, 178 = 64.5 %, were expelled spontaneously. The figures communicated regarding this by 13 authors vary considerably according to the patience of the doctor, and fluctuate between 3 and 73 %. The latter figure shows to what extent the powers of Nature may be trusted to deal with miscarriage. The hope of spontaneous expulsion may be still further considerably increased when the powers of Nature are strengthened by strong ecbolics; quinine, above all, has proved effective in my clinic, being administered in 3 forms, per os, intravenously and intramuscularly, each time 0.5 gram of a 25 % solution of quinine hydrochloride. *Henrard*, out of my 128 cases of feverish miscarriages treated with other ecbolics observed a spontaneous expulsion in 56 % and, out of 148 treated with quinine, 72 %.

Entire ova were spontaneously expelled in 4/5 of all cases, and

placentas in one-half of the cases; only where small remnants of miscarriage were retained did it fail completely.

Finally he formulates the following five principles:

1. Anyone having opportunity for bacteriological examination of the vaginal contents should effect it. If they show a pure culture or a predominant quantity of streptococci, particularly haemolytical, clearing should not be undertaken, or should only be carried out when the streptococci have disappeared; that is the bacteriological point of view in the treatment of feverish miscarriage.

2. Those who cannot or will not make a bacteriological examination should refrain from clearance in the feverish stage and only effect it 4 or 5 days after defervescence; one should not wait for more than 5 days for defervescence.

3. Spontaneous expulsion should be aimed at in all cases with the assistance of quinine.

4. Do not be misled by bleeding to hasty removal.

5. Complicated miscarriages should not be removed.

(*Deutsche Medizinische Wochenschrift,* Leipzig, **49:** No. 51, 21 Dec. 1923, p. 153—156. Summarized)

INDUCTION OF LABOUR BY QUININE AND PITUITRIN

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AT a meeting of the Edinburgh Obstetrical Society held on Wednesday, December 12th, with the President, Professor *B. P. Watson,* in the chair, a communication was read by *Dr. F. J. Browne* on the induction of labour by quinine and pituitrin. The speaker referred to the researches of *Oliver, Schafer, Dale, and Blair Bell* in connexion with the discovery of quinine and of its effect in producing uterine contractions, and to the investigations of *Fries, Haugh & Meyer, Stein & Dover,* and *Cron,* and of *B. P. Watson* on its employment in the induction of labour. In 1922 *Watson* had published the results obtained in a series of 195 cases, in 90 per cent. of which labour was successfully induced with no maternal mortality and a foetal death rate of 6 per cent.; none of these deaths could fairly be attributed to the use of pituitrin. The present communication was based on a series of forty-four cases; most of these had suffered from purulent vaginal discharges and were therefore unsuitable for induction by the ordinary mechanical methods. The technique followed in the majority of cases was that advised by *Watson* — namely, castor oil one ounce at 6 p.m., quinine hydrochloride gr. x at 7 p.m., enema at 8 p.m., quinine hydrochloride gr. x at 9 p.m., quinine hydrochloride gr. x at 12 midnight. If effective labour pains had not started twelve hours after the first dose of quinine — namely, by 7 a.m. — intramuscular injections of pituitrin were started, with a dose of $^1/_2$ c.cm., and repeating this every half-hour until labour commenced, or 3 c.cm., — that is, six injections — had been given. That was one full course. If labour pains did not start the treatment was repeated again after twenty-four hours. The quinine hydrochloride was given dissolved in min. x of dilute hydrochloric acid. The indications for its use included disproportion, primiparity at term, post-maturity, toxæmia, and hydramnios. Twenty-seven of the patients were primigravidae, the others multiparae. Twenty-three of the patients were at term, three were post-mature according to the estimated dates, and eighteen were premature. Out of the forty-four cases, forty were successful — that is, a little over 90 per cent. All the failures occurred in cases

where premature induction had been attempted. With regard to the time taken to start and complete labour, counting from the first dose of quinine, the time taken till the onset of labour averaged twenty-nine hours; the average duration of labour was sixteen hours. In premature cases the average time taken till the onset of labour was thirty-nine hours, the average duration of labour being nine hours. In spite of the numerous objections that had been urged against the use of pituitrin, the only unpleasant incidents the speaker had experienced were two cases of tetanic contraction of the uterus, in both cases the spasm was effectively controlled by chloroform, but in one case the child was stillborn. While twenty-six of the patients had suffered from purulent vaginal discharges, only three showed a rise of temperature in the puerperium, and in no case was this prolonged into a second day. In four cases the child had been stillborn; in only one case, however, a case of tetanic uterine contraction, could this be attributed to the pituitrin.

(*British Medical Journal*, London, Dec. 29, 1923. *Transactions of the Edinburgh Obstetrical Society*, 1923-1924, p. 25-33. *Edinburgh Medical Journal*, Feb. 1924)

QUININE IN OXYTOCIC TREATMENT

(LA QUININE DANS LA MÉDICATION OCYTOCIQUE)

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QUININE has been used for the last thirty years as a means of reinforcing uterine contractions. Some have used it with conviction, others with the idea that they were giving a harmless medicament so as to satisfy the patient and her family. In reality, quinine has an action. But its results are — above all else — linked up with its absorption. It sometimes happens that a quinine tablet is vomited absolutely intact a long time after having been swallowed.* Furthermore, when the quinine reaches the intestines, its absorption varies according to the individual, so much so, that its proportion in the blood is subject to variation. The concentration of quinine in the blood is higher in weak and anaemic people, as *Acton*[1] showed. According to this author, when the concentration of quinine in the blood reaches 1 in 150.000, it reinforces uterine contractions. Finally, just as with other oxytocic medicaments, the previous state of the tonus must be taken into consideration.

Clinical facts. — Ecbolic action.

The question whether quinine can produce abortion has been very much discussed. This point is of particular importance in malarial countries. Among the authors who have treated the subject, *Burdel* (1874) must be mentioned. *Burdel* declares that he is convinced of the non-abortive action of quinine, nay more, by stopping the malarial fever, this medicament contributes, if anything, to preventing abortion. Other doctors have seen cases in which the administration of quinine determined abortion or premature delivery, either producing at the same time severe intoxication phenomena, or without any accompanying phenomena. Finally, *Tarnier* and other authors have reported clear cases of abortion after ingestion of moderate doses of quinine, and they explain these facts by a kind of idiosyncrasy.

* I have used quinine with success in the form of suppositories.

Williamson,[2] associating castor oil in one dose, with several doses of quinine, induced delivery in 300 cases. But, according to him, it is the castor oil which starts labour, quinine simply increases the rhythm and the tonus.

2. *Oxytocic action.*

Quinine sulphate very often produces a reinforcement of the uterine contractions when lagging. *Schroeder, Auvard, Porak, Schwaab, Keim*, among others, have laid stress on this well-known point. The following history comes from my practice:

Mrs. H..., 21 years old, primipara, treated several times for troubles due to a certain degree of thyroid instability, begins labour in the night of the 20—21 March 1921 (323 days after the last catamenia), about midnight. Labour lags; at 1.45 a.m. and at 8 a.m. dilatation is of one finger; — at 3 p.m., one shilling; — at 11 p.m., 2 shilling; I prescribe 500 milligrams of quinine and at 2 a.m. on the 22nd March she gives birth to a boy weighing 6 lbs.

It is true that such accelerations of labour may happen spontaneously; in the present case however it seems that quinine improved the contraction, or that it produced a stronger contraction which brought on the complete flexion of the head, following which the rotation and descent of the head were completed.

These facts are not constant: Schwaab however speaks of a constant action, and *Cordes*, who used quinine to remove the ovular remains after abortion, says that he never had to perform any more curetting.

These are the optimists of quinine.

The following are a few figures which make it possible clearly to determine this point:

	Reinforcement	Decrease	No change
Hammond primiparae	35	2	1
Hammond multiparae	57	4	2
Vignes (unpublished cases)	6	1	8
Maurer	61	17	
Bachmann	91	64	

I add to these statistics a few details about my own figures.

Favourable cases

	Time of administration	State of dilatation	No. of hours necessary for termination
H	23	2 fingers	3
D (2nd child)	7	1 dollar	1.10
A*	55	small palm	5.— (forceps)
P	15	great palm	3.—
D (first child)	15.30	compl. dilation	1.20
M	10	ditto	0.45

Unfavourable cases

	Time of administration	State of dilatation	No. of hours necessary for termination	Complementary intervention
F	52	2 fingers	8	gas analgesia
W	15	1 dollar	5.45	forceps
O	11	1 dollar	5.45	morphine injection
N	29	small palm	8	forceps
M	25	ditto	13	do.
C	19	ditto	4	do.
T	16	great palm	3.50	no intervention
G		ditto	8	forceps
P	6.30	Compl. dilat.	2	forceps

Various statistics show that quinine has sometimes an inhibitory action (see above). I myself observed a very clear case:

Mrs. de M... (obs. 155), 20 years old, primipara; severe vomiting at beginning of pregnancy; increases in weight; sometimes has hallucinations; begins labour on July 5th 1921 in the morning, (283 days after last catamenia). — Child in L.O.A. — at 11 p.m. 2 fingers dilatation. — on July 6th at 5.30, a. m. 1 dollar — at 10.45 a. m. small palm — I prescribe 500 milligrams quinine — From then on complete calm till 5 p.m. when labour starts again. — Forceps application the next morning 3/4 hour past midnight. Here is a case where quinine had no action, and even seems to have delayed the labour. Very much surprised by this fact, I wondered if some tablet of antipyrine had not been given instead of quinine. Mr. *Charpentier*, resident pharmacist at the Lariboisière Hospital, was kind enough to analyse the unused capsules. They all gave clearly the reaction special to quinine.

The graphic data obtained by the recording of the contractions of several women show the same instability. *Rucker*[3], for instance, who

* Mrs. A. figures in this category, even though forceps were applied, because after quinine, satisfactory contractions appeared for a moment.

was successful in registering by internal hysterography the contraction of six women who had taken quinine, found that the action of this medicament varies very much. It sometimes distinctly reinforces, and sometimes it has no action whatever, may be owing to the method of introduction.

Contracture is exceptional after the use of quinine if it occurs at all. Instances of contracture have been found only exceptionally in women. *Tassius*, who used quinine, especially during the period of dilatation, has not had one case of continuous contracture in 194 cases. We must however point out two cases observed by *Beaugendre*[4], in which, after administration of quinine sulphate, the uterus remained tetanised for two hours without any effective labour (Medical Society of Rouen, Dec. 12th 1921).

However, if quinine is used intravenously or intramuscularly, the results are somewhat different, according to *Muschallik*[5]. This author obtained remarkable results: 93,5 % of success in 124 cases. He recommends the use of quinine in this form at all stages of delivery, but especially at the moment of expulsion of the after-birth. He tried the above mentioned injection in 50 cases, and drew the following conclusions: no danger either to mother or child. Tinnitus, visual disturbance, sensation of heat, bitter taste in mouth, are phenomena which must not be taken into account. The inconvenience of the method resides more in the frequency of spasmodic contractions, and the impossibility to regulate them, though the life of the child has never been in danger in the cases studied by the author. The best results have been obtained at the beginning of the delivery. *Stackosch*[6], *Werner*,[7] have been able by intravenous injection to increase the strength of the contractions, and even to start delivery. On the contrary, *Hinselmann*[8] using intravenous methods in the case of abortion had 21 expulsions and 12 failures.

This shows that, apart from the cases where there is a strong concentration of quinine in the blood, such as is produced by intravenous injections, it is exceptional to observe uterine contracture.

Physiological data.

It really seems that quinine acts directly on the muscular fibre of the uterus without passing through the nervous system. *Kurdinowski* settled this point, to which *O'Kamoto*[9] returned very recently, showing in particular that atropin does not modify its action.

Besides, this a fact of a general character. Not long ago, *Brody* showed that the action of quinine on the muscular fibre in general can easily be made evident on the striated muscle, and he saw that it

decreases the height of the contraction and especially diminishes the effect of contracting excitations while maintaining the rhythm.

The action of reinforcement of the uterine contraction is more constant in animals than in women. According to *Acton*, experimentally, quinine increases the contractions of the uterus which has been removed, and this happens both as regards the longitudinal and the circular fibres.

According to *O'Kamoto*, quinine inhibits the non-gravid uterus, and stimulates the gravid uterus because the distention of the fibres has rendered them sensitive to any kind of stimulant.

There is disagreement as to the effect of quinine on the tonus of the uterus. According to *Kurdinowsky's* experimental researches, quinine produces a considerable increase of the tonus, and his graphics are quite characteristic. But the action of quinine is not sufficiently tetanic to be dangerous to the foetus. However, if very strong doses are used uterine tetanus may be started. Experimenting on animals, *Acton* found that a strong contraction determines a tonic spasm, but this dose is very near the one which is toxic for the subject.

Attention must be drawn to the fact that the doses used in these various experiments were considerable. We saw, in human practice, that the reinforcement is far from being constant, and that contracture is uncommonly rare.

I will even go further and say that it was my impression that quinine in ordinary doses hastens the delivery by working against the contracture. The last of my cases in which quinine was successful were those of women whose labour was not progressing, who had weak contractions but painful intervals. Under the influence of quinine, the pains became more frequent, while they disappeared during the intervals. This is only an impression which needs clinical and experimental verification, but I should not be astonished if these facts were graphically translated by an unlevelling: lowering of the tonus, rise of the contraction cone. Inversely, in the cases where labour dragged owing to weak contractions and feeble tonus, I found that quinine stopped the contractions. Quinine is also inactive when it is used too soon, when contractility is still weak *(Rübsamen*[10]*)*.

The action of quinine has been discussed not as regards the uterus alone and *Gubler* was led to say that "quinine sulphate which has been considered in turn as exciting agent, a sedative, a tonic, and a narcotic, should not deserve all these contradictory epithets". *Turrettini*[11] recently recalled that: "Quinine has been considered in turn as stimulant, then as a depressant of the heart".

This action of quinine and of its isomer, quinidine, on the heart has

been studied very thoroughly during the last months. It is known that quinine diminishes fibrillations, as well as the excitability of the myocardium and the excitability of the accelerator sympathetic nerves. So that as *Turrettini* said in the above-mentioned article, quinine has its place in all the manifestations of cardiac hyper-excitability. It is probable that in the doses used by us in obstetric practice, quinine acts in the same manner on the uterus, thus deserving its old description of anti-spasmodic.

Another interesting fact is to be drawn from cardiac therapeutics: quinine acts only if the cardiac muscle possesses a certain degree of resistance. The same seems to be the case with the uterus, and the history of Mrs. de M... which we related above undoubtedly proves this. Generally, quinine does not accelerate the labour of a uterus which has good contractions; either it has no action or it delays the labour. These are small facts frequently observable if the trouble is taken to "observe" the circumstances of uterine contraction[12].

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EXPECTANT TREATMENT OF INCOMPLETE FEBRILE ABORTION

E. BOVIN, STOCKHOLM

THE author gives statistical evidence in support of his advocacy of expectant treatment for incomplete febrile abortion. Of 3,806 cases of abortion admitted to his hospital during the past eleven years 1,141 were cases of incomplete febrile abortion. In 623 of these cases the abortion was completed spontaneously, and the mortality was only 1.3 per cent. Among the 518 cases in which delivery was artificially completed there were 15 deaths, the mortality of 2.9 per cent. being more than twice as great as that with expectant treatment alone. This was abandoned on account of severe haemorrhage in 206 cases, among which there were 5 deaths. When expectant treatment had to be abandoned the mortality from artificial evacuation was much lower among the patients who had been afebrile for some days before the operation than among those who were still febrile. The author confirms *Winter's* observations that giving quinine frequently by the mouth often promotes the spontaneous completion of an abortion. He endorses *Latzko's* opinion that, if statistics based upon sufficiently large numbers are studied, the mortality from the active treatment of febrile abortion will be found to be approximately 50 per cent. greater than that from expectant treatment. The capacity of the uterus to expel its contents automatically has been much underrated.

(*Hygiea*, Stockholm, **85:** Dec. 31, 1923, p. 993-1008. Summary *British Medical Journal*, London, Feb. 23, 1924, p. 32)

THE ACTION OF QUININE ON THE PREGNANT UTERUS BY THE WATSON METHOD

(L'AZIONE DEL CHININO SULL'UTERO GRAVIDO SECONDO IL METODO DI WATSON)

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WATSON (*Transactions of the American Gynecological Society*, 1920) recommends again the use of quinine, as well in cases of abortion as in the period of expulsion, and he has furthermore insisted on the fact that quinine in the form of solution (subcutaneous injections) is more active than in powder form. According to *Watson's* article, the patient receives at first 30 grammes of castor oil by mouth, and then two hours later a subcutaneous injection of 65 centigrammes of quinine in a diluted solution of muriatic acid. If necessary, these injections are repeated twice at two hours interval.

The author applied *Watson's* method in various cases. The result was that it seems that quinine does not possess a special abortive action. Even in premature deliveries injections of quinine did not prove to be particularly active. On the contrary, quinine proved to be most efficacious in cases of weak contractions in normal delivery.

Besides ear ringing, the patients did not present any troubles. The children were not touched by this quinine medication.

(*Rassegna d'ostetricia e ginecologia*, Napoli, **32:** N. 7-9 July—Sept. 1923, p. 161. Summary *Zentralblatt für Gynäkologie*, Leipzig, **48:** N. 2, 17 May 1924, p. 1112)

PAINLESS CHILDBIRTH BY SYNERGISTIC METHODS

PRELIMINARY REPORT

JAMES T. GWATHMEY, E. P. DONOVAN, JOHN O'REAGAN, LELAND R. COWAN. NEW YORK, N. Y.

AFTER discussing the investigations of others regarding the action of ether and magnesium sulphate on gravidae, the writers, on the basis of investigations on more than 100 gravidae, (Lying-In Hospital, New York) communicate their results with their method, which is based on synergism of the above substances in the smallest effective quantity. During parturition in actual process (cervix admitting 2 fingers) subcutaneously 2 c.c. of a 25 % solution of magnesium sulphate with 0.01—0.015 gram of morphia (not necessary when using 50 % $MgSO_2$ solution). If necessary repeat 1—3 times, but without morphia. 1-2 hours later, (pains of 30 seconds duration every 4-5 minutes — cervix admits $2\frac{1}{2}$—$3\frac{1}{2}$ fingers) in the *Sims's* lateral position injection by means of a thin catheter with glass funnel placed on. The catheter is inserted 4 in. in the rectum. Instead of the funnel *Cowan* recommends a syringe: inject slowly during 2-3 pains. During the pains pressure by compresses on the perineum, to prevent return flow. Of the injection 120 grams (or twice 60) is used. Composition: Chin. hydrobrom. 0.6, alcohol 7.5, ether 75.0, Ol. oliv. 30.0 grams in $\frac{1}{2}$-1 hour p.i. analgesia begins.

Results: The pains were increased in 1 %, unaltered in 3 % and variously reduced to entire disappearance in 96 % of the cases. In 2% of the women malaise, in 4% thirst and in 8% vomiting. Labour was increased in 4 %, otherwise normal. With regard to post partum hemorrhage and mechanism of labour, there was no change (4% forceps, 96 % normal births).

Of the children 1 % had (not fatal) asphyxia, 2 % apnoea, and 97 % were normal.

(*American Journal of Obstetrics & Gynecology,* St. Louis. **6**: 1923, p. 456—466. Review *Zentralblatt für Gynäkologie,* Leipzig, **48**: N. 39, 27 Sept. 1924, p. 2158)

QUININE IN CASES OF ERYSIPELAS

To the editor of *The Lancet.*

SIR, — The use of *Warburg's* tincture in tropical countries for a large variety of ailments suggested to me the extended use of quinine in this country, and during the past 23 years I have substituted quinine for salicylate of Soda and never regretted having done so. In cases of erysipelas quinine acts like a charm, the patients feeling so well generally that their sole desire is to resume their duties irrespective of appearances. The local lesion is treated by quickly brushing over the affected area (and 1 inch beyond if possible an application made up of one part of tincture of iodine to seven parts of *Keith's* anaesthetic ether, once daily. The general treatment consists in giving orally, every two hours, 10 gr. of sulphate of quinine undissolved, 10 minims of spirit of chloroform, and ½ minim of essence of peppermint in 4oz. of cold milk. When the temperature and pulse become normal, or nearly so, reduce to every six hours.

Erysipelas is fortunately a rare disease nowadays and it is impossible to give statistics, as one can do in other diseases. Nevertheless, the results obtained during the past eleven years seem to justify anyone trying the above treatment, and I am convinced that they will not be disappointed.

I am, Sir, yours faithfully,

JOHN WISHART, M.D., D.Sc., F.L.S.

Newcastle-upon-Tyne,
Nov. 14th, 1924.

(*Lancet*, London, **207**: II, Nr. 21, Nov. 22, 1924, p. 1097)

TREATMENT OF PRURITUS ANI, VULVAE AND SCROTI

M. P. MOORER, M.D., ASHEVILLE, N. C., U.S.A.

UNDER thorough infiltration of the skin and subcutaneous tissue extending one-half inch beyond the area affected, with 0.5 per cent. quinin and urea hydrochlorid solution, itching is at once arrested; excoriations rapidly heal, and within a few days the skin resumes its normal smoothness and luster. Anesthesia, however, persists for from several days to as many weeks, and, at the expiration of this period, a second and sometimes a third infiltration is or may be required. It has not been necessary to employ a fourth infiltration in any case thus far treated, as the causative factor is searched for, and, if found, eliminated during the days of freedom from itching produced by this simple measure. Occasionally, one injection suffices, and the patient remains away for months; but he finally returns to have skin tabs removed or other operative rectal procedure which he was told in the first instance would be needed to insure permanent relief, attended to.

The technic consists in rendering the part clean with water, a good soap and a soft sponge; application of a solution of mercurochrome-220 soluble as an antiseptic, and the injection of a small area with 1 per cent. procain as a starter. The remainder of the diseased skin is then infiltrated, after which the underlying subcutaneous structure is ballooned out with quinin and urea hydrochlorid solution until the patient complains on resuming a chair that he is "sitting on a cushion." The precautions to be observed are as follows:

1. A decided neurotic element exists in all pruritus cases; therefore, it is wise to administer hypodermically one-fourth grain (0.01 gm.) of morphin before beginning this treatment, for the prevention of shock; otherwise, profound depression, resembling greatly the first few hours succeeding a grave surgical operation, is likely to follow.

2. Not more than 10 c.c. of 1 per cent. procain should be used, but quinin and urea hydrochlorid solution from 0.25 to 0.5 per cent. strength may be used in any necessary quantity, as much as 200 or

300 c.c. (quinin and urea hydrochlorid solution in greater than 0.5 strength may produce a slough or an unpleasant induration).

Results in a number of cases have been as good as with a *Ball* or *Lynch* operation, and infinitely better than with the cautery.

The pressure on the terminal nerves produced by the forcible injection of fluid in large amount brings about a temporary paralysis equal in duration to that produced by severance of their filaments with a knife, and to the mind of the average patient is much more acceptable.

(*Journal of the American Medical Association*, Chicago, **83**: No. 10, Sept. 6, 1924, p. 766)

QUININE AND BISMUTH PREPARATIONS IN THE TREATMENT OF SYPHILIS

(CHININWISMUTHPRAEPARATE BEI DER SYPHILISBEHANDLUNG)

DR. H. BOESCH, BERNE

Assistant at the Dermatological Clinic of the University

THE author, according to his paper: *Treatment of syphilis by bismuth preparations, at the Dermatological Clinic of the University of Berne, December 1921-April 1923,* used principally two preparations: Quinby (Iodo-bismuthate of quinine, formula Aubry, Cantin laboratory, Paris) and Trépol (Tartro-bismuthate of sodium and potassium, Chenal and Douilhet Laboratories, Paris).

Both preparations are given intramuscularly or deep subcutaneously. The intravenous method must be avoided because of the danger of embolism and the great toxicity. Quinby was given in the dose of 3 c.c. and Trépol in a dose of 2 c.c. The intervals were mostly three days, by way of exception 5 days. On an average the maximum total dose was 40 c.c. for Trépol and 60 c.c. for Quinby.

In the combined treatment with salvarsan and bismuth, the plan of the salvarsan-mercury treatment was generally followed. Salvarsan at intervals of about 5 days, and the bismuth composition twice a week, instead of the undiluted mercury salts, were injected. Care was taken not to make two injections — of mercury and bismuth — on the same day.

Summary.

1. The uncombined treatment of syphilis by Trépol and Quinby has demonstrated that we possess in these bismuth combinations two antiluetic agents which act energetically on the spirochete and quickly eradicate the clinical symptoms. Large condylomas and also very often adenopathies are favourably influenced. These preparations are certainly superior to mercury. Their efficacy is very nearly the same as that of salvarsan.

2. The combined salvarsan-bismuth treatment has a most favourable influence on all syphilitic skin symptoms, as well as on the sero-

reactions. The method of treatment enables us to decrease to no small extent the total dose of salvarsan, and on the whole is easily supported. It is, without any doubt, superior in most cases to the combined mercury-salvarsan treatment.

3. The accessory symptoms at the point of injection are in general less important than with the undiluted mercury preparations. The symptoms of the gums and kidneys are really not as dangerous as those due to mercury. Quinby gives hardly any disagreeable reactions. Trépol has a higher curative action than Quinby, but is also more toxic.

4. Absorption and excretion are quicker, in man, with bismuth than with mercury.

(Schweizerische Medizinische Wochenschrift, Basel, **53:** No. 46 and 47, 15 and 22 Nov. 1923, p. 1059—1064 and 1088—1092 Summarized)

QUININE AS A PROPHYLACTIC IN VENEREAL DISEASES

(CHININ ALS PROPHYLAKTIKUM BEI GESCHLECHTSKRANKHEITEN)

DR. M. MERZ, BASEL
Specialist in diseases of the skin

THE author, in his paper: *Individual prophylaxy in venereal diseases*, comes to the conclusion that it is preferable to apply the protective agency *before* the intercourse. The application of a prophylactic after the coitus is only of secondary importance. Nevertheless, this late application must still be considered as a useful and helpful measure and must therefore not be disregarded.

It also follows from the above that sublimate is to be preferred to oxycyanide. Mixtures of sublimate and oxycyanide cannot be used for chemical reasons. But it is possible to add to the sublimate some useful agent other than oxycyanide. Among the substances ranking for this purpose, quinine is the most appropriate. *Schereschewsky*, (Beiträge zur Pathologie & Therapie der Syphilis von *A. Neisser*, Berlin, 1911. — *Deutsche med. Wochenschrift*, 1913, 27) has proved the *intense parasitropic* — spirocheticidal — properties of quinine, the action of which on albumin is moreover favourable in this case. *Schereschewsky* successfully protected 5 monkeys from the infection by using a quinine preparation, although in the case of two of the animals, the preparation was applied only 25 and 30 minutes after the inoculation.

Prompted by the desire to utilise the bactericidal and parasitropic properties of mercury and quinine in combination and simultaneously, I myself made experiments in that direction, and satisfied myself of the favourable action of such combination. I obtained the best results with a colloidal suspension of mercury and quinine salts. (Quinine hydrochlor., Hydrargyr. bichloride, Aqua dest., Gelatin special. q.s. ad suspens. colloidal.). I was able to utilise to the full the disinfecting properties of these substances by embodying them in a mass containing no fat and prepared according to previously established requirements.

This mass contains 95 % of water and has the consistency of a salve. The conditions of dissociation are therefore nearly of the same value in this ground mass as in watery solutions. The protective mass thus combined forms on the mucosa a well-fixed coating, which acts at the same time as protective layer and as lubricant, and combines therefore the favourable properties of the salve with the maximum degree of dissociation. This association of mercury and quinine salts has the further advantage that it is not necessary to raise the proportion of sublimate to 0.3 % as has been done; because this concentration is very often followed by irritation of the mucosa and sometimes damage to the latter. Satisfactory results can still be obtained with a 0.02 % proportion of sublimate in the combination of mercury and quinine salts. The highest proportion of quinine which I used was 15 %. It was possible to reduce it to 2.5 %, still obtaining favourable results. The safest action without any irritation was obtained with a proportion of quinine and mercury about half-way between the given limits. Every one of the final experiments was made in this form.

I worked with this preparation for one year, and desire to give the following details as to the results of the tests:

The *bactericidal* action on gonococci is energetic and kills them even when applied in greatly diluted form.

The *parasitropic* — spirocheticidal — action is intense. All the animals used for experiments were, without any exception, kept free from infection by the prophylactic use of the preparation.

Prompted by these results, I resorted to *practical use*, and gave this prophylactic successively to about 100 men. I chose with that object men who, by their intellectual level, would understand the importance of the experiment, and who undertook to follow out exactly the instructions, and whose previous mode of life made an abstinence for a year improbable.

Among these men, who have been using the preparation about nine months, not one has come to me with a newly received infection.

Even if this result is not an absolute proof, the practical outcome is sufficiently uniform to preclude its being considered simply as a result of chance.

The preparation was in all cases used with the utmost readiness, as its manipulation is very simple; it is not betrayed either by odour or stains on the underwear. Further, it keeps well.

Theory, the experiments on animals and the result of practical application as above, alike justify the assumption that the above

combinations, together with the physical and chemical properties of the ground mass, represent a forward stride towards the solution of the problem of individual prophylaxis against veneral diseases, which is of such importance to public hygiene.

(*Schweizerische Medizinische Wochenschrift,* Basel, **53:** N. 47, 22 Nov. 1923, p. 1084—1088. Summarized).

QUININE AS A COATING FOR THE WOUND SURFACE OF THE AMPUTATED DENTAL PULP

(DAS CHININ ALS DECKMITTEL FÜR DIE WUNDFLÄCHE AMPUTIERTER ZAHNPULPEN)

PRELIMINARY COMMUNICATION

DR. FRANZ PÉTER, VIENNA

Assistant to the Dental Institute of the University

A lively debate was held about a year ago, at the Dentists' Societies of Vienna, on the subject of amputation of the dental pulp. The result was that the Viennese dentists were divided in three groups on this question:

1. Those who entirely dismissed the idea of amputation of the pulp (*Gottlieb, Schreier, Hauer*);

2. Those who entirely approved of the method and applied it in every case in the treatment of pulp partly or wholly exposed, and also of superficial pulpitis *(Kronfeld, Kneucker)*, and

3. Those who, although considering the extirpation method as the safest, yet in many cases (cavity of the neck in old people, hysterical and nervous patients, milk teeth, or very narrow root-canals of teeth with multiple roots) have, for a long time, used the amputation method. (*Weiser*).

I wrote in February 1923 that I firmly believed that the future lies with the amputation method.

Since then the Swiss author, *Lutz*, has published a very interesting study, which certainly marks progress in that line (I do not intend in this report to deal more extensively with this study; in Switzerland amputation is the prevalent method).

The attempt, made at the suggestion of Prof. *Wasicki* to substitute quinine for arsenious acid in dental practice, resulted in the following conclusions, which were published in the March number (1923) of *Zeitschrift für Stomatologie*, Vienna. The outcome of my researches was that the quinine paste did not possess the same power as the arsenious paste, of destroying the pulp, and therefore was not suited to take the place of arsenious acid.

I found however that quinine hydrochloride, a powerful antiseptic, possesses two more properties in relation to dental pulp, the first one being an absolute analgesic action and the second the power of limiting the necrosis of the pulp to a thin superficial layer only, while the deep layers remain alive for several months even after a prolonged action of the drug.

These properties of quinine have led me to think that quinine possesses just the qualities required for a coating for the stumps of amputated pulp. After removal of the crown pulp, leaving only the living amputated radicles in the canals, quinine will render these stumps numb, thus preventing the later occurrence of pain, and it will also, through its antiseptic properties, prevent the penetration of bacteria into the root-canals and keep the stumps alive, with the exception of the most superficial layer, a condition regarding which I refer the reader to the work of *Sicher*, who considers this live condition more advantageous and preferable than a mummified condition.

However closely this action of quinine approaches the object in view, yet the fact must not be overlooked that it is always hazardous to venture off the beaten track or to use a new agent in the methods of treatment of roots. Years must pass before we can reach a definite opinion, and this is the more difficult inasmuch as it is almost impossible to keep the patients of a clinical practice under observation for years. On the other hand, the responsibility is too great, teeth may be lost which would have been saved by other methods.

I was very careful in the first experiments with the new agent, and since February of this year, together with Mrs. Dr. *Edith Turmann*, partly at the Dental Institute, partly at the dental section of the *Pirquet* clinic, I have performed the amputation of the pulp on 68 cases with quinine paste (quinine hydrochloride with linseed oil and clove oil, mixed into a paste, and lately with linseed oil only).

We shall publish our results at the end of the first year, and besides the clinical description we shall lay stress on precise bacteriological and X-ray researches.

It can however be said already that the clinical evolution of these cases gives us the greatest expectations.

(*Zeitschrift fiir Stomatologie*, Vienna, **22**: N. 1, 1924, 45-46)

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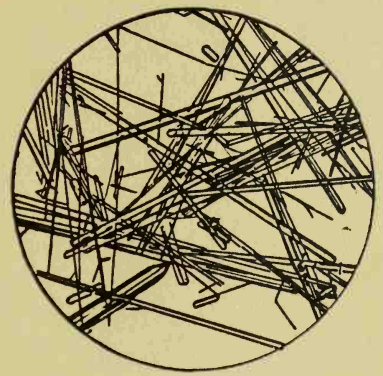

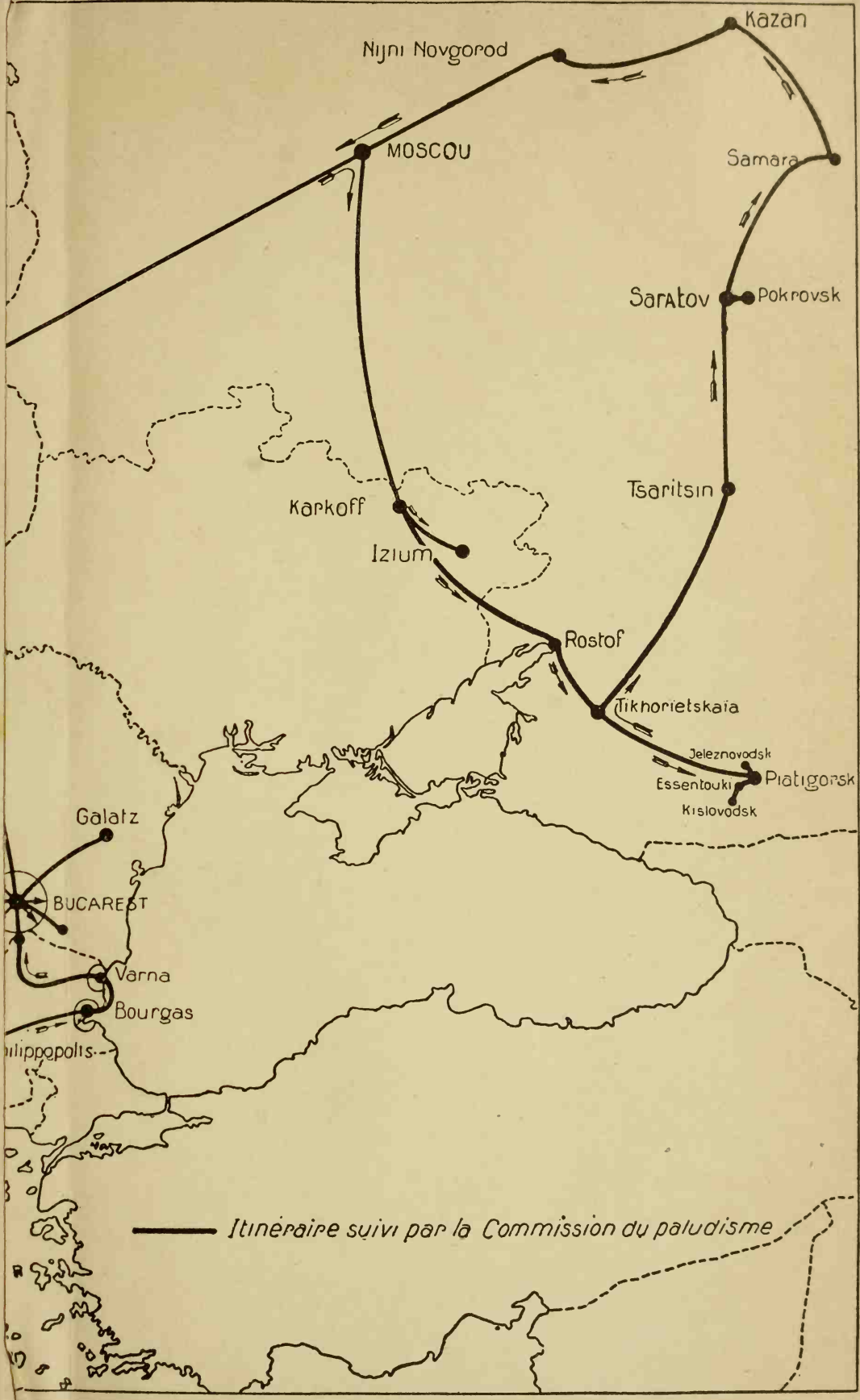
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